



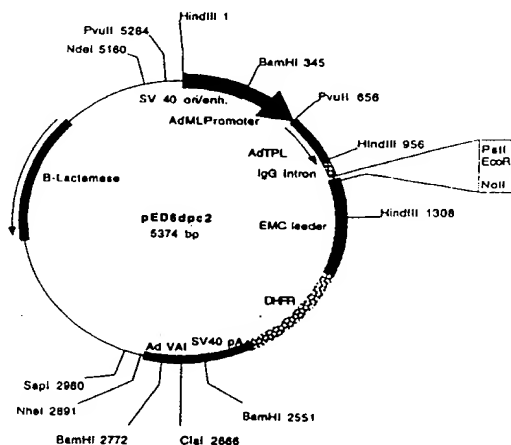
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(54) Title: SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

## (57) Abstract

Novel polynucleotides and the proteins encoded thereby are disclosed.



Plasmid name: pED6dpc2  
Plasmid size: 5374 bp

Comments/References: pED6dpc2 is derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning. SST cDNAs are cloned between EcoRI and NotI. pED vectors are described in Kaufman et al.(1991), NAR 19: 4485-4490.

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## SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

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This application is a continuation-in-part of Ser. No. 60/XXX,XXX (converted to a provisional application from non-provisional application 08/804,561), filed February 24, 1997, which is incorporated by reference herein.

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FIELD OF THE INVENTION

The present invention provides novel polynucleotides and proteins encoded by such polynucleotides, along with therapeutic, diagnostic and research utilities for these polynucleotides and proteins.

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BACKGROUND OF THE INVENTION

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Technology aimed at the discovery of protein factors (including e.g., cytokines, such as lymphokines, interferons, CSFs and interleukins) has matured rapidly over the past decade. The now routine hybridization cloning and expression cloning techniques clone novel polynucleotides "directly" in the sense that they rely on information directly related to the discovered protein (i.e., partial DNA/amino acid sequence of the protein in the case of hybridization cloning; activity of the protein in the case of expression cloning). More recent "indirect" cloning techniques such as signal sequence cloning, which isolates DNA sequences based on the presence of a now well-recognized secretory leader sequence motif, as well as various PCR-based or low stringency hybridization cloning techniques, have advanced the state of the art by making available large numbers of DNA/amino acid sequences for proteins that are known to have biological activity by virtue of their secreted nature in the case of leader sequence cloning, or by virtue of the cell or tissue source in the case of PCR-based techniques. It is to these proteins and the polynucleotides encoding them that the present invention is directed.

### SUMMARY OF THE INVENTION

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- 5 (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 65 to nucleotide 1270;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 1139 to nucleotide 1270;
- 10 (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 1011 to nucleotide 1216;
- (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BO114\_1 deposited under accession number ATCC 98333;
- 15 (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BO114\_1 deposited under accession number ATCC 98333;
- (g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BO114\_1 deposited under accession number ATCC 98333;
- ~~20 (h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BO114\_1 deposited under accession number ATCC 98333;~~
- (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2;
- (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity, the fragment comprising the amino acid sequence from amino acid 196 to amino acid 205 of SEQ ID NO:2;
- 25 (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;
- 30 (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and
- (m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:1 from nucleotide 65 to nucleotide 1270; the nucleotide sequence of SEQ ID NO:1 from nucleotide 1139 to nucleotide 1270; the nucleotide sequence of SEQ ID NO:1 from nucleotide 1011 to nucleotide 1216; the nucleotide sequence of the full-length protein coding sequence of clone BO114\_1 deposited under accession number ATCC 98333; or the nucleotide sequence of the mature protein coding sequence of clone BO114\_1 deposited under accession number ATCC 98333. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone BO114\_1 deposited under accession number ATCC 98333. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2 from amino acid 326 to amino acid 384.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:1.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:2;
  - (b) the amino acid sequence of SEQ ID NO:2 from amino acid 326 to amino acid 384;
  - (c) fragments of the amino acid sequence of SEQ ID NO:2 comprising the amino acid sequence from amino acid 196 to amino acid 205 of SEQ ID NO:2; and
  - (d) the amino acid sequence encoded by the cDNA insert of clone BO114\_1 deposited under accession number ATCC 98333;
- the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:2 or the amino acid sequence of SEQ ID NO:2 from amino acid 326 to amino acid 384.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 418 to nucleotide 582;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 508 to nucleotide 582;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 1 to nucleotide 555;

5 (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CD311\_2 deposited under accession number ATCC 98333;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CD311\_2 deposited under accession number ATCC 98333;

10 (g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CD311\_2 deposited under accession number ATCC 98333;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CD311\_2 deposited under accession number ATCC 98333;

15 (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity, the fragment comprising the amino acid sequence from amino acid 22 to amino acid 31 of SEQ ID NO:4;

20 (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

25 (m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:3 from nucleotide 418 to nucleotide 582; the nucleotide sequence of SEQ ID NO:3 from nucleotide 508 to nucleotide 582; the nucleotide sequence of SEQ ID NO:3 from nucleotide 1 to nucleotide 555; the nucleotide sequence of the full-length protein coding sequence of clone CD311\_2 deposited under accession number ATCC 98333; or the nucleotide sequence of the mature protein coding sequence of clone CD311\_2 deposited under accession number ATCC 98333. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of

clone CD311\_2 deposited under accession number ATCC 98333. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 46.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ  
5 ID NO:3.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:4;
- 10 (b) the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 46;
- (c) fragments of the amino acid sequence of SEQ ID NO:4 comprising the amino acid sequence from amino acid 22 to amino acid 31 of SEQ ID NO:4; and
- (d) the amino acid sequence encoded by the cDNA insert of clone  
15 CD311\_2 deposited under accession number ATCC 98333;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:4 or the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 46.

In one embodiment, the present invention provides a composition comprising an  
20 isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 191 to nucleotide 1756;
- 25 (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 254 to nucleotide 1756;
- (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 1 to nucleotide 604;
- (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CG279\_1 deposited under accession  
30 number ATCC 98333;
- (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CG279\_1 deposited under accession number ATCC 98333;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CG279\_1 deposited under accession number ATCC 98333;

5 (h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CG279\_1 deposited under accession number ATCC 98333;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6;

10 (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity, the fragment comprising the amino acid sequence from amino acid 256 to amino acid 265 of SEQ ID NO:6;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

15 (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:5 from nucleotide 191 to nucleotide 1756; the nucleotide sequence of SEQ ID NO:5 from nucleotide 254 to nucleotide 1756; the nucleotide sequence of SEQ ID NO:5 from

20 nucleotide 1 to nucleotide 604; the nucleotide sequence of the full-length protein coding sequence of clone CG279\_1 deposited under accession number ATCC 98333; or the nucleotide sequence of the mature protein coding sequence of clone CG279\_1 deposited under accession number ATCC 98333. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone CG279\_1 deposited under accession number ATCC 98333. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 138.

25 Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:5.

30 In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:6;



(b) the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 138;

(c) fragments of the amino acid sequence of SEQ ID NO:6 comprising the amino acid sequence from amino acid 256 to amino acid 265 of SEQ ID NO:6; and

(d) the amino acid sequence encoded by the cDNA insert of clone CG279\_1 deposited under accession number ATCC 98333; the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:6 or the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 138.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 226 to nucleotide 948;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 1128 to nucleotide 1601;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CJ424\_9 deposited under accession number ATCC 98333;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CJ424\_9 deposited under accession number ATCC 98333;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CJ424\_9 deposited under accession number ATCC 98333;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CJ424\_9 deposited under accession number ATCC 98333;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:8;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity, the fragment comprising the amino acid sequence from amino acid 115 to amino acid 124 of SEQ ID NO:8;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

5 (l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:7 from nucleotide 226 to nucleotide 948; the nucleotide sequence of SEQ ID NO:7 from nucleotide 1128 to nucleotide 1601; the nucleotide sequence of the full-length protein  
10 coding sequence of clone CJ424\_9 deposited under accession number ATCC 98333; or the nucleotide sequence of the mature protein coding sequence of clone CJ424\_9 deposited under accession number ATCC 98333. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone CJ424\_9 deposited under accession number ATCC 98333.

15 Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:7.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

20 (a) the amino acid sequence of SEQ ID NO:8;

(b) fragments of the amino acid sequence of SEQ ID NO:8 comprising the amino acid sequence from amino acid 115 to amino acid 124 of SEQ ID NO:8; and

(c) the amino acid sequence encoded by the cDNA insert of clone  
25 CJ424\_9 deposited under accession number ATCC 98333;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:8.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

30 (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 137 to nucleotide 895;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 1488 to nucleotide 2274;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CR930\_1 deposited under accession number ATCC 98333;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CR930\_1 deposited under accession number ATCC 98333;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CR930\_1 deposited under accession number ATCC 98333;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CR930\_1 deposited under accession number ATCC 98333;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:10;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity, the fragment comprising the amino acid sequence from amino acid 121 to amino acid 130 of SEQ ID NO:10;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:9 from nucleotide 137 to nucleotide 895; the nucleotide sequence of SEQ ID NO:9 from nucleotide 1488 to nucleotide 2274; the nucleotide sequence of the full-length protein coding sequence of clone CR930\_1 deposited under accession number ATCC 98333; or the nucleotide sequence of the mature protein coding sequence of clone CR930\_1 deposited under accession number ATCC 98333. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone CR930\_1 deposited under accession number ATCC 98333.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:9.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:10;
- 5 (b) fragments of the amino acid sequence of SEQ ID NO:10 comprising the amino acid sequence from amino acid 121 to amino acid 130 of SEQ ID NO:10; and
- (c) the amino acid sequence encoded by the cDNA insert of clone CR930\_1 deposited under accession number ATCC 98333;
- 10 the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:10.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- 15 (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 494 to nucleotide 973;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 611 to nucleotide 973;
- 20 (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 521 to nucleotide 940;
- (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone DA306\_4 deposited under accession number ATCC 98333;
- 25 (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone DA306\_4 deposited under accession number ATCC 98333;
- (g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone DA306\_4 deposited under accession number ATCC 98333;
- 30 (h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone DA306\_4 deposited under accession number ATCC 98333;
- (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity, the fragment comprising the amino acid sequence from amino acid 75 to amino acid 84 of SEQ ID NO:12;

5 (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

10 (m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:11 from nucleotide 494 to nucleotide 973; the nucleotide sequence of SEQ ID NO:11 from nucleotide 611 to nucleotide 973; the nucleotide sequence of SEQ ID NO:11 from nucleotide 521 to nucleotide 940; the nucleotide sequence of the full-length protein coding  
15 sequence of clone DA306\_4 deposited under accession number ATCC 98333; or the nucleotide sequence of the mature protein coding sequence of clone DA306\_4 deposited under accession number ATCC 98333. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone DA306\_4 deposited under accession number ATCC 98333. In yet other preferred  
20 embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12 from amino acid 11 to amino acid 149.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:11.

25 In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:12;

30 (b) the amino acid sequence of SEQ ID NO:12 from amino acid 11 to amino acid 149;

(c) fragments of the amino acid sequence of SEQ ID NO:12 comprising the amino acid sequence from amino acid 75 to amino acid 84 of SEQ ID NO:12; and

- (d) the amino acid sequence encoded by the cDNA insert of clone DA306\_4 deposited under accession number ATCC 98333; the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:12 or the amino acid sequence of SEQ ID NO:12 from amino acid 11 to amino acid 149.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 2295 to nucleotide 2594;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 1867 to nucleotide 2372;
- (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone DG76\_1 deposited under accession number ATCC 98333;
- (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone DG76\_1 deposited under accession number ATCC 98333;
- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone DG76\_1 deposited under accession number ATCC 98333;
- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone DG76\_1 deposited under accession number ATCC 98333;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:14;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity, the fragment comprising the amino acid sequence from amino acid 45 to amino acid 54 of SEQ ID NO:14;
- (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
- (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:13 from nucleotide 2295 to nucleotide 2594; the nucleotide sequence of SEQ ID NO:13 from nucleotide 1867 to nucleotide 2372; the nucleotide sequence of the full-length protein coding sequence of clone DG76\_1 deposited under accession number ATCC 98333; or the nucleotide sequence of the mature protein coding sequence of clone DG76\_1 deposited under accession number ATCC 98333. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone DG76\_1 deposited under accession number ATCC 98333. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:14 from amino acid 1 to amino acid 26.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:13.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:14;
  - (b) the amino acid sequence of SEQ ID NO:14 from amino acid 1 to amino acid 26;
  - (c) fragments of the amino acid sequence of SEQ ID NO:14 comprising the amino acid sequence from amino acid 45 to amino acid 54 of SEQ ID NO:14; and
  - (d) the amino acid sequence encoded by the cDNA insert of clone DG76\_1 deposited under accession number ATCC 98333;
- the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:14 or the amino acid sequence of SEQ ID NO:14 from amino acid 1 to amino acid 26.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 394 to nucleotide 522;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 1 to nucleotide 476;

5 (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone DO19\_1 deposited under accession number ATCC 98333;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone DO19\_1 deposited under accession number ATCC 98333;

10 (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone DO19\_1 deposited under accession number ATCC 98333;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone DO19\_1 deposited under accession number ATCC 98333;

15 (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity, the fragment comprising the amino acid sequence from amino acid 16 to amino acid 25 of SEQ ID NO:16;

20 (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

25 (l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:15 from nucleotide 394 to nucleotide 522; the nucleotide sequence of SEQ ID NO:15 from nucleotide 1 to nucleotide 476; the nucleotide sequence of the full-length protein coding sequence of clone DO19\_1 deposited under accession number ATCC 98333; or the nucleotide sequence of the mature protein coding sequence of clone DO19\_1 deposited under accession number ATCC 98333. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone DO19\_1 deposited under accession number ATCC 98333. In yet other preferred



embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16 from amino acid 1 to amino acid 27.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:15.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:16;
- (b) the amino acid sequence of SEQ ID NO:16 from amino acid 1 to amino acid 27;
- (c) fragments of the amino acid sequence of SEQ ID NO:16 comprising the amino acid sequence from amino acid 16 to amino acid 25 of SEQ ID NO:16; and
- (d) the amino acid sequence encoded by the cDNA insert of clone DO19\_1 deposited under accession number ATCC 98333;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:16 or the amino acid sequence of SEQ ID NO:16 from amino acid 1 to amino acid 27.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 262 to nucleotide 654;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 322 to nucleotide 654;
- (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 1 to nucleotide 618;
- (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone EQ219\_1 deposited under accession number ATCC 98333;
- (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone EQ219\_1 deposited under accession number ATCC 98333;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone EQ219\_1 deposited under accession number ATCC 98333;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone EQ219\_1 deposited under accession number ATCC 98333;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:18;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 having biological activity, the fragment comprising the amino acid sequence from amino acid 60 to amino acid 69 of SEQ ID NO:18;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:17 from nucleotide 262 to nucleotide 654; the nucleotide sequence of SEQ ID NO:17 from nucleotide 322 to nucleotide 654; the nucleotide sequence of SEQ ID NO:17 from nucleotide 1 to nucleotide 618; the nucleotide sequence of the full-length protein coding sequence of clone EQ219\_1 deposited under accession number ATCC 98333; or the nucleotide sequence of the mature protein coding sequence of clone EQ219\_1 deposited under accession number ATCC 98333. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone EQ219\_1 deposited under accession number ATCC 98333. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:18 from amino acid 1 to amino acid 119.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:17.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:18;
- (b) the amino acid sequence of SEQ ID NO:18 from amino acid 1 to amino acid 119;
- (c) fragments of the amino acid sequence of SEQ ID NO:18 comprising the amino acid sequence from amino acid 60 to amino acid 69 of SEQ ID NO:18; and
- (d) the amino acid sequence encoded by the cDNA insert of clone EQ219\_1 deposited under accession number ATCC 98333;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:18 or the amino acid sequence of SEQ ID NO:18 from amino acid 1 to amino acid 119.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 74 to nucleotide 310;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 125 to nucleotide 310;
- (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 1 to nucleotide 338;
- (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone FG340\_1 deposited under accession number ATCC 98333;
- (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone FG340\_1 deposited under accession number ATCC 98333;
- (g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone FG340\_1 deposited under accession number ATCC 98333;
- (h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone FG340\_1 deposited under accession number ATCC 98333;
- (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:20;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:20 having biological activity, the fragment comprising the amino acid sequence from amino acid 34 to amino acid 43 of SEQ ID NO:20;

5 (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

10 (m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:19 from nucleotide 74 to nucleotide 310; the nucleotide sequence of SEQ ID NO:19 from nucleotide 125 to nucleotide 310; the nucleotide sequence of SEQ ID NO:19 from nucleotide 1 to nucleotide 338; the nucleotide sequence of the full-length protein coding  
15 sequence of clone FG340\_1 deposited under accession number ATCC 98333; or the nucleotide sequence of the mature protein coding sequence of clone FG340\_1 deposited under accession number ATCC 98333. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone FG340\_1 deposited under accession number ATCC 98333. In yet other preferred  
20 embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:20 from amino acid 1 to amino acid 75.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:19.

25 In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:20;

30 (b) the amino acid sequence of SEQ ID NO:20 from amino acid 1 to amino acid 75;

(c) fragments of the amino acid sequence of SEQ ID NO:20 comprising the amino acid sequence from amino acid 34 to amino acid 43 of SEQ ID NO:20; and

(d) the amino acid sequence encoded by the cDNA insert of clone FG340\_1 deposited under accession number ATCC 98333; the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:20 or the amino acid sequence of SEQ ID NO:20 from amino acid 1 to amino acid 75.

In certain preferred embodiments, the polynucleotide is operably linked to an expression control sequence. The invention also provides a host cell, including bacterial, yeast, insect and mammalian cells, transformed with such polynucleotide compositions. Also provided by the present invention are organisms that have enhanced, reduced, or modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein.

Processes are also provided for producing a protein, which comprise:

- (a) growing a culture of the host cell transformed with such polynucleotide compositions in a suitable culture medium; and
- (b) purifying the protein from the culture.

The protein produced according to such methods is also provided by the present invention. Preferred embodiments include those in which the protein produced by such process is a mature form of the protein.

Protein compositions of the present invention may further comprise a pharmaceutically acceptable carrier. Compositions comprising an antibody which specifically reacts with such protein are also provided by the present invention.

Methods are also provided for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition comprising a protein of the present invention and a pharmaceutically acceptable carrier.

#### BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A and 1B are schematic representations of the pED6 and pNOTs vectors, respectively, used for deposit of clones disclosed herein.

#### DETAILED DESCRIPTION

##### ISOLATED PROTEINS AND POLYNUCLEOTIDES

Nucleotide and amino acid sequences, as presently determined, are reported below for each clone and protein disclosed in the present application. The nucleotide

sequence of each clone can readily be determined by sequencing of the deposited clone in accordance with known methods. The predicted amino acid sequence (both full-length and mature) can then be determined from such nucleotide sequence. The amino acid sequence of the protein encoded by a particular clone can also be determined by  
5 expression of the clone in a suitable host cell, collecting the protein and determining its sequence. For each disclosed protein applicants have identified what they have determined to be the reading frame best identifiable with sequence information available at the time of filing.

As used herein a "secreted" protein is one which, when expressed in a suitable host  
10 cell, is transported across or through a membrane, including transport as a result of signal sequences in its amino acid sequence. "Secreted" proteins include without limitation proteins secreted wholly (e.g., soluble proteins) or partially (e.g., receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins which are transported across the membrane of the endoplasmic reticulum.

15

#### Clone "BO114\_1"

A polynucleotide of the present invention has been identified as clone "BO114\_1". BO114\_1 was isolated from a human adult retina cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was  
20 identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. BO114\_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "BO114\_1 protein").

The nucleotide sequence of BO114\_1 as presently determined is reported in SEQ  
25 ID NO:1. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the BO114\_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:2. Amino acids 346 to 358 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 359, or are a transmembrane domain.

30 The EcoRI/NotI restriction fragment obtainable from the deposit containing clone BO114\_1 should be approximately 1600 bp.

The nucleotide sequence disclosed herein for BO114\_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. BO114\_1 demonstrated at least some similarity with sequences

identified as AA430329 (zw20e04.r1 Soares ovary tumor NbHOT Homo sapiens cDNA clone 769854 5' similar to contains element MER22 repetitive element), H00825 (yj31b05.r1 Homo sapiens cDNA clone 150321 5'), H12557 (yj12c09.r1 Homo sapiens cDNA clone 148528 5'), W53899 (md09c01.r1 Soares mouse embryo NbME13.5 14.5 Mus musculus cDNA), and Z82202 (Human DNA sequence \*\*\* SEQUENCING IN PROGRESS \*\*\* from clone 34P24). Based upon sequence similarity, BO114\_1 proteins and each similar protein or peptide may share at least some activity.

#### Clone "CD311\_2"

10 A polynucleotide of the present invention has been identified as clone "CD311\_2". CD311\_2 was isolated from a human fetal brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. CD311\_2 is a full-length  
15 clone, including the entire coding sequence of a secreted protein (also referred to herein as "CD311\_2 protein").

The nucleotide sequence of CD311\_2 as presently determined is reported in SEQ ID NO:3. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the CD311\_2 protein corresponding to the foregoing  
20 nucleotide sequence is reported in SEQ ID NO:4. Amino acids 18 to 30 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 31, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone CD311\_2 should be approximately 2400 bp.

25 The nucleotide sequence disclosed herein for CD311\_2 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. CD311\_2 demonstrated at least some similarity with sequences identified as H17421 (ym40d12.s1 Homo sapiens cDNA clone 50810 3'), H20618 (ym47b01.r1 Homo sapiens cDNA clone 51411 5'), and U70476 (Rattus norvegicus cationic  
30 amino acid transporter-1 (CAT-1) mRNA, complete cds). Based upon sequence similarity, CD311\_2 proteins and each similar protein or peptide may share at least some activity.

Clone "CG279\_1"

A polynucleotide of the present invention has been identified as clone "CG279\_1". CG279\_1 was isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. CG279\_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "CG279\_1 protein").

The nucleotide sequence of CG279\_1 as presently determined is reported in SEQ ID NO:5. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the CG279\_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:6. Amino acids 9 to 21 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 22, or are a transmembrane domain. Amino acids 43 to 55 are a possible leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 56, or are a transmembrane domain

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone CG279\_1 should be approximately 3940 bp.

The nucleotide sequence disclosed herein for CG279\_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. CG279\_1 demonstrated at least some similarity with sequences identified as AA568111 (nf13c05.s1 NCI\_CGAP\_Pr1 Homo sapiens cDNA clone IMAGE:913640), D63222 (Human placenta cDNA 5'-end GEN-508F12), H64777 (yu62h09.r1 Homo sapiens cDNA clone 238433 5' similar to contains Alu repetitive element; contains TAR1 repetitive element), M17262 (Human prothrombin (F2) gene, complete cds, and Alu and KpnI repeats), Q39724 (Expressed Sequence Tag human gene marker EST00316), U14685 (Gorilla gorilla Alu-Sb2 repeat, clone GO-14), U14691 (Gorilla gorilla Alu-Sb2 repeat, clone GOI2-11), and W15458 (zc19h02.s1 Soares parathyroid tumor NbHPA Homo sapiens cDNA clone 322803 3'). The predicted amino acid sequence disclosed herein for CG279\_1 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted CG279\_1 protein demonstrated at least some similarity to sequences identified as D25215 (KIAA0032 [Homo sapiens]), M15530 (B-cell growth factor [Homo sapiens]), and R95913 (Neural thread protein). Based upon sequence similarity, CG279\_1 proteins and each similar



protein or peptide may share at least some activity. The TopPredII computer program predicts three potential transmembrane domains within the CG279\_1 protein sequence, centered around amino acids 30, 250, and 390 of SEQ ID NO:6, respectively. The nucleotide sequence of CG279\_1 indicates that it may contain one or more Alu repetitive elements.

#### Clone "CJ424\_9"

A polynucleotide of the present invention has been identified as clone "CJ424\_9". CJ424\_9 was isolated from a human fetal brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. CJ424\_9 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "CJ424\_9 protein").

The nucleotide sequence of CJ424\_9 as presently determined is reported in SEQ ID NO:7. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the CJ424\_9 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:8.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone CJ424\_9 should be approximately 1650 bp.

The nucleotide sequence disclosed herein for CJ424\_9 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. CJ424\_9 demonstrated at least some similarity with sequences identified as AB000215 (*Rattus norvegicus* cca1 mRNA, complete cds) and R83763 (yp16f06.s1 *Homo sapiens* cDNA clone 187619 3'). The predicted amino acid sequence disclosed herein for CJ424\_9 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted CJ424\_9 protein demonstrated at least some similarity to sequences identified as AB000215 (CCA1 protein [*Rattus norvegicus*]) and M59465 (A20 [*Homo sapiens*]). Based upon sequence similarity, CJ424\_9 proteins and each similar protein or peptide may share at least some activity.

#### Clone "CR930\_1"

A polynucleotide of the present invention has been identified as clone "CR930\_1". CR930\_1 was isolated from a human adult testes cDNA library using methods which are

selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. CR930\_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "CR930\_1 protein").

The nucleotide sequence of CR930\_1 as presently determined is reported in SEQ ID NO:9. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the CR930\_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:10.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone CR930\_1 should be approximately 2400 bp.

The nucleotide sequence disclosed herein for CR930\_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. CR930\_1 demonstrated at least some similarity with sequences identified as AA058338 (zk82e08.s1 Soares pregnant uterus NbHPU Homo sapiens cDNA clone 489350 3'), N54229 yz03f05.r1 Homo sapiens cDNA clone), R89733 (ym99e10.r1 Homo sapiens cDNA clone 167082 5'), and W60141 (zc94f06.s1 Pancreatic Islet Homo sapiens cDNA clone 338819 3'). The predicted amino acid sequence disclosed herein for CR930\_1 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted CR930\_1 protein demonstrated at least some similarity to sequences identified as a *C. elegans* ORF (open reading frame) (U21324) that is weakly similar to *S. cerevisiae* CBP3 protein precursor (SP:CBP3\_YEAST, P21560), a mitochondrial membrane protein. Based upon sequence similarity, CR930\_1 proteins and each similar protein or peptide may share at least some activity.

#### Clone "DA306\_4"

A polynucleotide of the present invention has been identified as clone "DA306\_4". DA306\_4 was isolated from a human adult placenta cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. DA306\_4 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "DA306\_4 protein").

The nucleotide sequence of DA306\_4 as presently determined is reported in SEQ ID NO:11. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the DA306\_4 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:12. Amino acids 27 to 39 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 40, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone DA306\_4 should be approximately 2800 bp.

The nucleotide sequence disclosed herein for DA306\_4 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. DA306\_4 demonstrated at least some similarity with sequences identified as AA397398 (nc65a07.r1 NCI CGAP Pr1 Homo sapiens cDNA clone 771444), AL008629 (Human DNA sequence \*\*\* SEQUENCING IN PROGRESS \*\*\* from clone 197O17; HTGS phase 1), D78769 (Human placenta cDNA 5'-end GEN-512A03), M19364 (Human gamma-B-crystallin (gamma 1-2) and gamma-C-crystallin (gamma 2-1) genes, complete cds), N29380 (yw97f09.s1 Homo sapiens cDNA clone 260201 3'), N47928 (yw97f09.r1 Homo sapiens cDNA clone 260201 5'), Z83745 (Human DNA sequence from PAC 453A3 contains EST and STS), and Z83848 (Human DNA sequence \*\*\* SEQUENCING IN PROGRESS \*\*\* from clone 57A13; HTGS phase 1). The predicted amino acid sequence disclosed herein for DA306\_4 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted DA306\_4 protein demonstrated at least some similarity to sequences identified as M12140 (envelope protein [Homo sapiens]), M19051 (pol protein [Mus musculus]), R75189 (Osteoinductive retrovirus RFB-14 pol gene product), U88902 (integrase [Homo sapiens]). Based upon sequence similarity, DA306\_4 proteins and each similar protein or peptide may share at least some activity. The nucleotide sequence of DA306\_4 indicates that it may contain a CpG island repeat region.

#### Clone "DG76\_1"

A polynucleotide of the present invention has been identified as clone "DG76\_1". DG76\_1 was isolated from a human adult placenta cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. DG76\_1 is a full-length clone,

including the entire coding sequence of a secreted protein (also referred to herein as "DG76\_1 protein").

The nucleotide sequence of DG76\_1 as presently determined is reported in SEQ ID NO:13. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the DG76\_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:14.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone DG76\_1 should be approximately 3300 bp.

The nucleotide sequence disclosed herein for DG76\_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. DG76\_1 demonstrated at least some similarity with sequences identified as AA044352 (zk54c01.r1 Soares pregnant uterus NbHPU Homo sapiens cDNA clone 486624 5') and N57171 (yw90f09.r1 Homo sapiens cDNA clone 259529 5'). Based upon sequence similarity, DG76\_1 proteins and each similar protein or peptide may share at least some activity. The TopPredII computer program predicts two potential transmembrane domains within the DG76\_1 protein sequence, centered amino acids 15 and 80 of SEQ ID NO:14, respectively. The nucleotide sequence of DG76\_1 indicates that it may contain a MER repeat region.

#### Clone "DO19\_1"

A polynucleotide of the present invention has been identified as clone "DO19\_1". DO19\_1 was isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. DO19\_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "DO19\_1 protein").

The nucleotide sequence of DO19\_1 as presently determined is reported in SEQ ID NO:15. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the DO19\_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:16.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone DO19\_1 should be approximately 700 bp.

The nucleotide sequence disclosed herein for DO19\_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. DO19\_1 demonstrated at least some similarity with sequences identified as AA339440 (EST44546 Fetal brain I Homo sapiens cDNA 5' end). Based upon  
5 sequence similarity, DO19\_1 proteins and each similar protein or peptide may share at least some activity. The nucleotide sequence of DO19\_1 indicates that it may contain one or more MER20 repetitive elements.

#### Clone "EQ219\_1"

10 A polynucleotide of the present invention has been identified as clone "EQ219\_1". EQ219\_1 was isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. EQ219\_1 is a full-length  
15 clone, including the entire coding sequence of a secreted protein (also referred to herein as "EQ219\_1 protein").

The nucleotide sequence of EQ219\_1 as presently determined is reported in SEQ ID NO:17. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the EQ219\_1 protein corresponding to the foregoing  
20 nucleotide sequence is reported in SEQ ID NO:18. Amino acids 8 to 20 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 21, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone EQ219\_1 should be approximately 800 bp.

25 The nucleotide sequence disclosed herein for EQ219\_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. EQ219\_1 demonstrated at least some similarity with sequences identified as AA400429 (zu62a09.s1 Soares testis NHT Homo sapiens cDNA clone 742552 3'). Based upon sequence similarity, EQ219\_1 proteins and each similar protein or peptide  
30 may share at least some activity. The TopPredII computer program predicts an additional potential transmembrane domain within the EQ219\_1 protein sequence, centered around amino acid 90 of SEQ ID NO:18.

Clone "FG340\_1"

A polynucleotide of the present invention has been identified as clone "FG340\_1". FG340\_1 was isolated from a human adult brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was  
5 identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. FG340\_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "FG340\_1 protein").

The nucleotide sequence of FG340\_1 as presently determined is reported in SEQ  
10 ID NO:19. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the FG340\_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:20. Amino acids 5 to 17 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 18, or are a transmembrane domain.

15 The EcoRI/NotI restriction fragment obtainable from the deposit containing clone FG340\_1 should be approximately 900 bp.

The nucleotide sequence disclosed herein for FG340\_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. FG340\_1 demonstrated at least some similarity with sequences  
20 identified as N59424 (y51g05.s1 Homo sapiens cDNA clone 246296 3'). The FG340\_1 nucleotide sequence has an interesting simple "TG" nucleotide repeat from basepair 96 to basepair 131 of SEQ ID NO:19. This region encodes a Cys-Val repeat in the FG340\_1 protein. Similar Cys-Val stretches are found in the amino termini of X52164 (Q300 protein (AA 1-77) [Mus musculus]) and M37679 (Ig heavy chain precursor [Mus musculus]).  
25 Based upon sequence similarity, FG340\_1 proteins and each similar protein or peptide may share at least some activity.

Deposit of Clones

Clones BO114\_1, CD311\_2, CG279\_1, CJ424\_9, CR930\_1, DA306\_4, DG76\_1,  
30 DO19\_1, EQ219\_1, and FG340\_1 were deposited on February 20, 1997 with the American Type Culture Collection as an original deposit under the Budapest Treaty and were given the accession number ATCC 98333, from which each clone comprising a particular polynucleotide is obtainable. All restrictions on the availability to the public of the

deposited material will be irrevocably removed upon the granting of the patent, except for the requirements specified in 37 C.F.R. § 1.808(b).

Each clone has been transfected into separate bacterial cells (*E. coli*) in this composite deposit. Each clone can be removed from the vector in which it was deposited by performing an EcoRI/NotI digestion (5' site, EcoRI; 3' site, NotI) to produce the appropriate fragment for such clone. Each clone was deposited in either the pED6 or pNOTs vector depicted in Fig. 1. The pED6dpc2 vector ("pED6") was derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning (Kaufman *et al.*, 1991, *Nucleic Acids Res.* 19: 4485-4490); the pNOTs vector was derived from pMT2 (Kaufman *et al.*, 1989, *Mol. Cell. Biol.* 9: 946-958) by deletion of the DHFR sequences, insertion of a new polylinker, and insertion of the M13 origin of replication in the ClaI site. In some instances, the deposited clone can become "flipped" (i.e., in the reverse orientation) in the deposited isolate. In such instances, the cDNA insert can still be isolated by digestion with EcoRI and NotI. However, NotI will then produce the 5' site and EcoRI will produce the 3' site for placement of the cDNA in proper orientation for expression in a suitable vector. The cDNA may also be expressed from the vectors in which they were deposited.

Bacterial cells containing a particular clone can be obtained from the composite deposit as follows:

An oligonucleotide probe or probes should be designed to the sequence that is known for that particular clone. This sequence can be derived from the sequences provided herein, or from a combination of those sequences. The sequence of the oligonucleotide probe that was used to isolate each full-length clone is identified below, and should be most reliable in isolating the clone of interest.

<u>Clone</u>	<u>Probe Sequence</u>
BO114_1	SEQ ID NO:21
CD311_2	SEQ ID NO:22
CG279_1	SEQ ID NO:23
CJ424_9	SEQ ID NO:24
CR930_1	SEQ ID NO:25
DA306_4	SEQ ID NO:26
DG76_1	SEQ ID NO:27

DO19\_1

SEQ ID NO:28

EQ219\_1

SEQ ID NO:29

FG340\_1

SEQ ID NO:30

5 In the sequences listed above which include an N at position 2, that position is occupied in preferred probes/primers by a biotinylated phosphoramidite residue rather than a nucleotide (such as , for example, that produced by use of biotin phosphoramidite (1-dimethoxytrityloxy-2-(N-biotinyl-4-aminobutyl)-propyl-3-O-(2-cyanoethyl)-(N,N-diisopropyl)-phosphoramidite) (Glen Research, cat. no. 10-1953)).

10 The design of the oligonucleotide probe should preferably follow these parameters:

(a) It should be designed to an area of the sequence which has the fewest ambiguous bases ("N's"), if any;

(b) It should be designed to have a  $T_m$  of approx. 80 ° C (assuming 2° for each A or T and 4 degrees for each G or C).

15 The oligonucleotide should preferably be labeled with g-<sup>32</sup>P ATP (specific activity 6000 Ci/mmole) and T4 polynucleotide kinase using commonly employed techniques for labeling oligonucleotides. Other labeling techniques can also be used. Unincorporated label should preferably be removed by gel filtration chromatography or other established  
20 methods. The amount of radioactivity incorporated into the probe should be quantitated by measurement in a scintillation counter. Preferably, specific activity of the resulting probe should be approximately 4e+6 dpm/pmole.

The bacterial culture containing the pool of full-length clones should preferably be thawed and 100 µl of the stock used to inoculate a sterile culture flask containing 25 ml  
25 of sterile L-broth containing ampicillin at 100 µg/ml. The culture should preferably be grown to saturation at 37°C, and the saturated culture should preferably be diluted in fresh L-broth. Aliquots of these dilutions should preferably be plated to determine the dilution and volume which will yield approximately 5000 distinct and well-separated colonies on solid bacteriological media containing L-broth containing ampicillin at 100  
30 µg/ml and agar at 1.5% in a 150 mm petri dish when grown overnight at 37°C. Other known methods of obtaining distinct, well-separated colonies can also be employed.

Standard colony hybridization procedures should then be used to transfer the colonies to nitrocellulose filters and lyse, denature and bake them.



The filter is then preferably incubated at 65°C for 1 hour with gentle agitation in 6X SSC (20X stock is 175.3 g NaCl/liter, 88.2 g Na citrate/liter, adjusted to pH 7.0 with NaOH) containing 0.5% SDS, 100 µg/ml of yeast RNA, and 10 mM EDTA (approximately 10 mL per 150 mm filter). Preferably, the probe is then added to the hybridization mix at a concentration greater than or equal to 1e+6 dpm/mL. The filter is then preferably incubated at 65°C with gentle agitation overnight. The filter is then preferably washed in 500 mL of 2X SSC/0.5% SDS at room temperature without agitation, preferably followed by 500 mL of 2X SSC/0.1% SDS at room temperature with gentle shaking for 15 minutes. A third wash with 0.1X SSC/0.5% SDS at 65°C for 30 minutes to 1 hour is optional. The filter is then preferably dried and subjected to autoradiography for sufficient time to visualize the positives on the X-ray film. Other known hybridization methods can also be employed.

The positive colonies are picked, grown in culture, and plasmid DNA isolated using standard procedures. The clones can then be verified by restriction analysis, hybridization analysis, or DNA sequencing.

Fragments of the proteins of the present invention which are capable of exhibiting biological activity are also encompassed by the present invention. Fragments of the protein may be in linear form or they may be cyclized using known methods, for example, as described in H.U. Saragovi, *et al.*, Bio/Technology 10, 773-778 (1992) and in R.S. McDowell, *et al.*, J. Amer. Chem. Soc. 114, 9245-9253 (1992), both of which are incorporated herein by reference. Such fragments may be fused to carrier molecules such as immunoglobulins for many purposes, including increasing the valency of protein binding sites. For example, fragments of the protein may be fused through "linker" sequences to the Fc portion of an immunoglobulin. For a bivalent form of the protein, such a fusion could be to the Fc portion of an IgG molecule. Other immunoglobulin isotypes may also be used to generate such fusions. For example, a protein - IgM fusion would generate a decavalent form of the protein of the invention.

The present invention also provides both full-length and mature forms of the disclosed proteins. The full-length form of the such proteins is identified in the sequence listing by translation of the nucleotide sequence of each disclosed clone. The mature form of such protein may be obtained by expression of the disclosed full-length polynucleotide (preferably those deposited with ATCC) in a suitable mammalian cell or other host cell. The sequence of the mature form of the protein may also be determinable from the amino acid sequence of the full-length form.

The present invention also provides genes corresponding to the polynucleotide sequences disclosed herein. "Corresponding genes" are the regions of the genome that are transcribed to produce the mRNAs from which cDNA polynucleotide sequences are derived and may include contiguous regions of the genome necessary for the regulated expression of such genes. Corresponding genes may therefore include but are not limited to coding sequences, 5' and 3' untranslated regions, alternatively spliced exons, introns, promoters, enhancers, and silencer or suppressor elements. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials. An "isolated gene" is a gene that has been separated from the adjacent coding sequences, if any, present in the genome of the organism from which the gene was isolated.

Organisms that have enhanced, reduced, or modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein are provided. The desired change in gene expression can be achieved through the use of antisense polynucleotides or ribozymes that bind and/or cleave the mRNA transcribed from the gene (Albert and Morris, 1994, *Trends Pharmacol. Sci.* 15(7): 250-254; Lavarosky *et al.*, 1997, *Biochem. Mol. Med.* 62(1): 11-22; and Hampel, 1998, *Prog. Nucleic Acid Res. Mol. Biol.* 58: 1-39; all of which are incorporated by reference herein). Transgenic animals that have multiple copies of the gene(s) corresponding to the polynucleotide sequences disclosed herein, preferably produced by transformation of cells with genetic constructs that are stably maintained within the transformed cells and their progeny, are provided. Transgenic animals that have modified genetic control regions that increase or reduce gene expression levels, or that change temporal or spatial patterns of gene expression, are also provided (see European Patent No. 0 649 464 B1, incorporated by reference herein). In addition, organisms are provided in which the gene(s) corresponding to the polynucleotide sequences disclosed herein have been partially or completely inactivated, through insertion of extraneous sequences into the corresponding gene(s) or through deletion of all or part of the corresponding gene(s). Partial or complete gene inactivation can be accomplished through insertion, preferably followed by imprecise excision, of transposable elements (Plasterk, 1992, *Bioessays* 14(9): 629-633; Zwaal *et al.*, 1993, *Proc. Natl. Acad. Sci. USA* 90(16): 7431-7435; Clark *et al.*, 1994, *Proc. Natl. Acad. Sci. USA* 91(2): 719-722; all of which are incorporated by reference herein), or through homologous recombination,

preferably detected by positive/negative genetic selection strategies (Mansour *et al.*, 1988, *Nature* 336: 348-352; U.S. Patent Nos. 5,464,764; 5,487,992; 5,627,059; 5,631,153; 5,614,396; 5,616,491; and 5,679,523; all of which are incorporated by reference herein). These organisms with altered gene expression are preferably eukaryotes and more preferably are mammals. Such organisms are useful for the development of non-human models for the study of disorders involving the corresponding gene(s), and for the development of assay systems for the identification of molecules that interact with the protein product(s) of the corresponding gene(s).

Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such domains from sequence information.

Proteins and protein fragments of the present invention include proteins with amino acid sequence lengths that are at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of a disclosed protein and have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with that disclosed protein, where sequence identity is determined by comparing the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Also included in the present invention are proteins and protein fragments that contain a segment preferably comprising 8 or more (more preferably 20 or more, most preferably 30 or more) contiguous amino acids that shares at least 75% sequence identity (more preferably, at least 85% identity; most preferably at least 95% identity) with any such segment of any of the disclosed proteins.

Species homologs of the disclosed polynucleotides and proteins are also provided by the present invention. As used herein, a "species homologue" is a protein or polynucleotide with a different species of origin from that of a given protein or polynucleotide, but with significant sequence similarity to the given protein or polynucleotide, as determined by those of skill in the art. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species. Preferably, species homologs are those isolated from mammalian species.

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous, or related to that encoded by the polynucleotides .

5       The invention also includes polynucleotides with sequences complementary to those of the polynucleotides disclosed herein.

10       The present invention also includes polynucleotides capable of hybridizing under reduced stringency conditions, more preferably stringent conditions, and most preferably highly stringent conditions, to polynucleotides described herein. Examples of stringency conditions are shown in the table below: highly stringent conditions are those that are at least as stringent as, for example, conditions A-F; stringent conditions are at least as stringent as, for example, conditions G-L; and reduced stringency conditions are at least as stringent as, for example, conditions M-R.

Stringency Condition	Polynucleotide Hybrid	Hybrid Length (bp) <sup>1</sup>	Hybridization Temperature and Buffer <sup>1</sup>	Wash Temperature and Buffer <sup>1</sup>
A	DNA:DNA	≥ 50	65°C; 1xSSC -or- 42°C; 1xSSC, 50% formamide	65°C; 0.3xSSC
B	DNA:DNA	<50	T <sub>h</sub> *; 1xSSC	T <sub>h</sub> *; 1xSSC
C	DNA:RNA	≥ 50	67°C; 1xSSC -or- 45°C; 1xSSC, 50% formamide	67°C; 0.3xSSC
D	DNA:RNA	<50	T <sub>D</sub> *; 1xSSC	T <sub>D</sub> *; 1xSSC
E	RNA:RNA	≥ 50	70°C; 1xSSC -or- 50°C; 1xSSC, 50% formamide	70°C; 0.3xSSC
F	RNA:RNA	<50	T <sub>F</sub> *; 1xSSC	T <sub>F</sub> *; 1xSSC
G	DNA:DNA	≥ 50	65°C; 4xSSC -or- 42°C; 4xSSC, 50% formamide	65°C; 1xSSC
H	DNA:DNA	<50	T <sub>H</sub> *; 4xSSC	T <sub>H</sub> *; 4xSSC
I	DNA:RNA	≥ 50	67°C; 4xSSC -or- 45°C; 4xSSC, 50% formamide	67°C; 1xSSC
J	DNA:RNA	<50	T <sub>I</sub> *; 4xSSC	T <sub>I</sub> *; 4xSSC
K	RNA:RNA	≥ 50	70°C; 4xSSC -or- 50°C; 4xSSC, 50% formamide	67°C; 1xSSC
L	RNA:RNA	<50	T <sub>L</sub> *; 2xSSC	T <sub>L</sub> *; 2xSSC
M	DNA:DNA	≥ 50	50°C; 4xSSC -or- 40°C; 6xSSC, 50% formamide	50°C; 2xSSC
N	DNA:DNA	<50	T <sub>N</sub> *; 6xSSC	T <sub>N</sub> *; 6xSSC
O	DNA:RNA	≥ 50	55°C; 4xSSC -or- 42°C; 6xSSC, 50% formamide	55°C; 2xSSC
P	DNA:RNA	<50	T <sub>P</sub> *; 6xSSC	T <sub>P</sub> *; 6xSSC
Q	RNA:RNA	≥ 50	60°C; 4xSSC -or- 45°C; 6xSSC, 50% formamide	60°C; 2xSSC
R	RNA:RNA	<50	T <sub>R</sub> *; 4xSSC	T <sub>R</sub> *; 4xSSC

<sup>1</sup>: The hybrid length is that anticipated for the hybridized region(s) of the hybridizing polynucleotides. When hybridizing a polynucleotide to a target polynucleotide of unknown sequence, the hybrid length is assumed to be that of the hybridizing polynucleotide. When polynucleotides of known sequence are hybridized, the hybrid length can be determined by aligning the sequences of the polynucleotides and identifying the region or regions of optimal sequence complementarity.

<sup>2</sup>: SSPE (1xSSPE is 0.15M NaCl, 10mM NaH<sub>2</sub>PO<sub>4</sub>, and 1.25mM EDTA, pH 7.4) can be substituted for SSC (1xSSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after hybridization is complete.

\*T<sub>h</sub> - T<sub>F</sub>: The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature (T<sub>m</sub>) of the hybrid, where T<sub>m</sub> is determined according to the following equations. For hybrids less than 18 base pairs in length, T<sub>m</sub>(°C) = 2(# of A + T bases) + 4(# of G + C bases). For hybrids between 18 and 49 base pairs in length, T<sub>m</sub>(°C) = 81.5 + 16.6(log<sub>10</sub>[Na<sup>+</sup>]) + 0.41(%G+C) - (600/N), where N is the number of bases in the hybrid, and [Na<sup>+</sup>] is the concentration of sodium ions in the hybridization buffer ([Na<sup>+</sup>] for 1xSSC = 0.165 M).

- Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E.F. Fritsch, and T. Maniatis, 1989, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, chapters 9 and 11, and *Current Protocols in Molecular Biology*, 1995, F.M. Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

Preferably, each such hybridizing polynucleotide has a length that is at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of the polynucleotide of the present invention to which it hybridizes, and has at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with the polynucleotide of the present invention to which it hybridizes, where sequence identity is determined by comparing the sequences of the hybridizing polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps.

The isolated polynucleotide of the invention may be operably linked to an expression control sequence such as the pMT2 or pED expression vectors disclosed in Kaufman *et al.*, *Nucleic Acids Res.* 19, 4485-4490 (1991), in order to produce the protein recombinantly. Many suitable expression control sequences are known in the art. General methods of expressing recombinant proteins are also known and are exemplified in R. Kaufman, *Methods in Enzymology* 185, 537-566 (1990). As defined herein "operably linked" means that the isolated polynucleotide of the invention and an expression control sequence are situated within a vector or cell in such a way that the protein is expressed by a host cell which has been transformed (transfected) with the ligated polynucleotide/expression control sequence.

A number of types of cells may act as suitable host cells for expression of the protein. Mammalian host cells include, for example, monkey COS cells, Chinese Hamster Ovary (CHO) cells, human kidney 293 cells, human epidermal A431 cells, human Colo205 cells, 3T3 cells, CV-1 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from *in vitro* culture of primary tissue, primary explants, HeLa cells, mouse L cells, BHK, HL-60, U937, HaK or Jurkat cells.

Alternatively, it may be possible to produce the protein in lower eukaryotes such as yeast or in prokaryotes such as bacteria. Potentially suitable yeast strains include *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, *Kluyveromyces* strains, *Candida*, or any yeast strain capable of expressing heterologous proteins. Potentially suitable bacterial strains include *Escherichia coli*, *Bacillus subtilis*, *Salmonella typhimurium*, or any bacterial

strain capable of expressing heterologous proteins. If the protein is made in yeast or bacteria, it may be necessary to modify the protein produced therein, for example by phosphorylation or glycosylation of the appropriate sites, in order to obtain the functional protein. Such covalent attachments may be accomplished using known chemical or enzymatic methods.

The protein may also be produced by operably linking the isolated polynucleotide of the invention to suitable control sequences in one or more insect expression vectors, and employing an insect expression system. Materials and methods for baculovirus/insect cell expression systems are commercially available in kit form from, *e.g.*, Invitrogen, San Diego, California, U.S.A. (the MaxBac® kit), and such methods are well known in the art, as described in Summers and Smith, Texas Agricultural Experiment Station Bulletin No. 1555 (1987), incorporated herein by reference. As used herein, an insect cell capable of expressing a polynucleotide of the present invention is "transformed."

The protein of the invention may be prepared by culturing transformed host cells under culture conditions suitable to express the recombinant protein. The resulting expressed protein may then be purified from such culture (*i.e.*, from culture medium or cell extracts) using known purification processes, such as gel filtration and ion exchange chromatography. The purification of the protein may also include an affinity column containing agents which will bind to the protein; one or more column steps over such affinity resins as concanavalin A-agarose, heparin-toyopearl® or Cibacrom blue 3GA Sepharose®; one or more steps involving hydrophobic interaction chromatography using such resins as phenyl ether, butyl ether, or propyl ether; or immunoaffinity chromatography.

Alternatively, the protein of the invention may also be expressed in a form which will facilitate purification. For example, it may be expressed as a fusion protein, such as those of maltose binding protein (MBP), glutathione-S-transferase (GST) or thioredoxin (TRX). Kits for expression and purification of such fusion proteins are commercially available from New England BioLab (Beverly, MA), Pharmacia (Piscataway, NJ) and InVitrogen, respectively. The protein can also be tagged with an epitope and subsequently purified by using a specific antibody directed to such epitope. One such epitope ("Flag") is commercially available from Kodak (New Haven, CT).

Finally, one or more reverse-phase high performance liquid chromatography (RP-HPLC) steps employing hydrophobic RP-HPLC media, *e.g.*, silica gel having pendant

methyl or other aliphatic groups, can be employed to further purify the protein. Some or all of the foregoing purification steps, in various combinations, can also be employed to provide a substantially homogeneous isolated recombinant protein. The protein thus purified is substantially free of other mammalian proteins and is defined in accordance with the present invention as an "isolated protein."

The protein of the invention may also be expressed as a product of transgenic animals, e.g., as a component of the milk of transgenic cows, goats, pigs, or sheep which are characterized by somatic or germ cells containing a nucleotide sequence encoding the protein.

The protein may also be produced by known conventional chemical synthesis. Methods for constructing the proteins of the present invention by synthetic means are known to those skilled in the art. The synthetically-constructed protein sequences, by virtue of sharing primary, secondary or tertiary structural and/or conformational characteristics with proteins may possess biological properties in common therewith, including protein activity. Thus, they may be employed as biologically active or immunological substitutes for natural, purified proteins in screening of therapeutic compounds and in immunological processes for the development of antibodies.

The proteins provided herein also include proteins characterized by amino acid sequences similar to those of purified proteins but into which modification are naturally provided or deliberately engineered. For example, modifications in the peptide or DNA sequences can be made by those skilled in the art using known techniques. Modifications of interest in the protein sequences may include the alteration, substitution, replacement, insertion or deletion of a selected amino acid residue in the coding sequence. For example, one or more of the cysteine residues may be deleted or replaced with another amino acid to alter the conformation of the molecule. Techniques for such alteration, substitution, replacement, insertion or deletion are well known to those skilled in the art (see, e.g., U.S. Patent No. 4,518,584). Preferably, such alteration, substitution, replacement, insertion or deletion retains the desired activity of the protein.

Other fragments and derivatives of the sequences of proteins which would be expected to retain protein activity in whole or in part and may thus be useful for screening or other immunological methodologies may also be easily made by those skilled in the art given the disclosures herein. Such modifications are believed to be encompassed by the present invention.



## USES AND BIOLOGICAL ACTIVITY

The polynucleotides and proteins of the present invention are expected to exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

### Research Uses and Utilities

The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which

the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

#### Nutritional Uses

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

#### Cytokine and Cell Proliferation/Differentiation Activity

A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays

for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

5 The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: *Current Protocols in Immunology*, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 10 7, Immunologic studies in Humans); Takai et al., *J. Immunol.* 137:3494-3500, 1986; Bertagnolli et al., *J. Immunol.* 145:1706-1712, 1990; Bertagnolli et al., *Cellular Immunology* 133:327-341, 1991; Bertagnolli, et al., *J. Immunol.* 149:3778-3783, 1992; Bowman et al., *J. Immunol.* 152: 1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node 15 cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon  $\gamma$ , Schreiber, R.D. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

Assays for proliferation and differentiation of hematopoietic and lymphopoietic 20 cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., *J. Exp. Med.* 173:1205-1211, 1991; Moreau et al., *Nature* 25 336:690-692, 1988; Greenberger et al., *Proc. Natl. Acad. Sci. U.S.A.* 80:2931-2938, 1983; Measurement of mouse and human interleukin 6 - Nordan, R. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., *Proc. Natl. Acad. Sci. U.S.A.* 83:1857-1861, 1986; Measurement of human Interleukin 11 - Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; 30 Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

#### Immune Stimulating or Suppressing Activity

A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases caused by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitus, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for

example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), *e.g.*, preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (*e.g.*, B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or

tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA-4Ig fusion proteins *in vivo* as described in Lenschow *et al.*, Science 257:789-792 (1992) and Turka *et al.*, Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function *in vivo* on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythematosus in MRL/lpr/lpr mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of

viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells *in vitro* with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the *in vitro* activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells *in vivo*.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (*e.g.*, sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected *ex vivo* with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection *in vivo*.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (*e.g.*, a cytoplasmic-domain truncated portion) of an MHC class I  $\alpha$  chain protein and  $\beta_2$  microglobulin protein or an MHC class II  $\alpha$  chain protein and an MHC class II  $\beta$  chain protein to thereby express MHC class I or MHC class II proteins on the cell surface.

Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Bowman et al., J. Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: *In vitro* antibody production, Mond, J.J. and Brunswick, M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter



7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad. Sci. USA 88:7548-7551, 1991.

#### Hematopoiesis Regulating Activity

A protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent

myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either *in-vivo* or *ex-vivo* (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. *Cellular Biology* 15:141-151, 1995; Keller et al., *Molecular and Cellular Biology*, 13:473-486, 1993; McClanahan et al., *Blood* 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M.G. In *Culture of Hematopoietic Cells*. R.I. Freshney, et al. eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., *Proc. Natl. Acad. Sci. USA* 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In *Culture of Hematopoietic Cells*. R.I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., *Experimental Hematology* 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In *Culture of Hematopoietic Cells*. R.I. Freshney, et al. eds. Vol pp. 1-21, Wiley-Liss, Inc., New York, NY. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In *Culture of Hematopoietic Cells*. R.I. Freshney, et al. eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland,

H.J. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

#### Tissue Growth Activity

5 A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

10 A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. *De novo* bone formation induced by an osteogenic agent contributes to the repair of  
15 congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce  
20 differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

25 Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and  
30 other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. *De novo* tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of

congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce  
5 differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors *ex vivo* for return *in vivo* to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in  
10 the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, *i.e.* for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve  
15 tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present  
20 ~~invention include mechanical and traumatic disorders, such as spinal cord disorders, head~~ trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of  
25 non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac)  
30 and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

5 A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

10 Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon); International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium ).

15 Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

#### Activin/Inhibin Activity

20 A protein of the present invention may also exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin  $\alpha$  family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals  
25 and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin- $\beta$  group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example,  
30 United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., *Endocrinology* 91:562-572, 1972; Ling et al., *Nature* 321:779-782, 1986; Vale et al., *Nature* 321:776-779, 1986; Mason et al., *Nature* 318:659-663, 1985; Forage et al., *Proc. Natl. Acad. Sci. USA* 83:3091-3095, 1986.

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#### Chemotactic/Chemokinetic Activity

A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells.

- 10 Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses
- 15 against the tumor or infecting agent.

- A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population
- 20 of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

- Assays for chemotactic activity (which will identify proteins that induce or prevent
- 25 chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: *Current Protocols in Immunology*, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene
- 30 Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. *J. Clin. Invest.* 95:1370-1376, 1995; Lind et al. *APMIS* 103:140-146, 1995; Muller et al. *Eur. J. Immunol.* 25: 1744-1748; Gruber et al. *J. of Immunol.* 152:5860-5867, 1994; Johnston et al. *J. of Immunol.* 153: 1762-1768, 1994.

### Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

### Receptor/Ligand Activity

A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene Publishing Associates and

Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 5 1995.

#### Anti-Inflammatory Activity

Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in 10 the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat 15 inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting 20 from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

#### Cadherin/Tumor Invasion Suppressor Activity

Cadherins are calcium-dependent adhesion molecules that appear to play major 25 roles during development, particularly in defining specific cell types. Loss or alteration of normal cadherin expression can lead to changes in cell adhesion properties linked to tumor growth and metastasis. Cadherin malfunction is also implicated in other human diseases, such as pemphigus vulgaris and pemphigus foliaceus (auto-immune blistering skin diseases), Crohn's disease, and some developmental abnormalities.

30 The cadherin superfamily includes well over forty members, each with a distinct pattern of expression. All members of the superfamily have in common conserved extracellular repeats (cadherin domains), but structural differences are found in other parts of the molecule. The cadherin domains bind calcium to form their tertiary structure and thus calcium is required to mediate their adhesion. Only a few amino acids in the



first cadherin domain provide the basis for homophilic adhesion; modification of this recognition site can change the specificity of a cadherin so that instead of recognizing only itself, the mutant molecule can now also bind to a different cadherin. In addition, some cadherins engage in heterophilic adhesion with other cadherins.

5 E-cadherin, one member of the cadherin superfamily, is expressed in epithelial cell types. Pathologically, if E-cadherin expression is lost in a tumor, the malignant cells become invasive and the cancer metastasizes. Transfection of cancer cell lines with polynucleotides expressing E-cadherin has reversed cancer-associated changes by returning altered cell shapes to normal, restoring cells' adhesiveness to each other and to  
10 their substrate, decreasing the cell growth rate, and drastically reducing anchorage-independent cell growth. Thus, reintroducing E-cadherin expression reverts carcinomas to a less advanced stage. It is likely that other cadherins have the same invasion suppressor role in carcinomas derived from other tissue types. Therefore, proteins of the present invention with cadherin activity, and polynucleotides of the present invention  
15 encoding such proteins, can be used to treat cancer. Introducing such proteins or polynucleotides into cancer cells can reduce or eliminate the cancerous changes observed in these cells by providing normal cadherin expression.

Cancer cells have also been shown to express cadherins of a different tissue type than their origin, thus allowing these cells to invade and metastasize in a different tissue  
20 in the body. Proteins of the present invention with cadherin activity, and polynucleotides of the present invention encoding such proteins, can be substituted in these cells for the inappropriately expressed cadherins, restoring normal cell adhesive properties and reducing or eliminating the tendency of the cells to metastasize.

Additionally, proteins of the present invention with cadherin activity, and  
25 polynucleotides of the present invention encoding such proteins, can be used to generate antibodies recognizing and binding to cadherins. Such antibodies can be used to block the adhesion of inappropriately expressed tumor-cell cadherins, preventing the cells from forming a tumor elsewhere. Such an anti-cadherin antibody can also be used as a marker for the grade, pathological type, and prognosis of a cancer, i.e. the more progressed the  
30 cancer, the less cadherin expression there will be, and this decrease in cadherin expression can be detected by the use of a cadherin-binding antibody.

Fragments of proteins of the present invention with cadherin activity, preferably a polypeptide comprising a decapeptide of the cadherin recognition site, and polynucleotides of the present invention encoding such protein fragments, can also be used

to block cadherin function by binding to cadherins and preventing them from binding in ways that produce undesirable effects. Additionally, fragments of proteins of the present invention with cadherin activity, preferably truncated soluble cadherin fragments which have been found to be stable in the circulation of cancer patients, and polynucleotides  
5 encoding such protein fragments, can be used to disturb proper cell-cell adhesion.

Assays for cadherin adhesive and invasive suppressor activity include, without limitation, those described in: Hortsch et al. *J Biol Chem* 270 (32): 18809-18817, 1995; Miyaki et al. *Oncogene* 11: 2547-2552, 1995; Ozawa et al. *Cell* 63: 1033-1038, 1990.

#### 10 Tumor Inhibition Activity

In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or  
15 tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth.

#### ~~20 Other Activities~~

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height,  
25 weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or circadian cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein,  
30 carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic

lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen  
5 in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

### ADMINISTRATION AND DOSING

10 A protein of the present invention (from whatever source derived, including without limitation from recombinant and non-recombinant sources) may be used in a pharmaceutical composition when combined with a pharmaceutically acceptable carrier. Such a composition may also contain (in addition to protein and a carrier) diluents, fillers,  
15 salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s). The characteristics of the carrier will depend on the route of administration. The pharmaceutical composition of the invention may also contain cytokines, lymphokines, or other hematopoietic factors such as M-CSF, GM-CSF, TNF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11,  
20 IL-12, IL-13, IL-14, IL-15, IFN, TNF0, TNF1, TNF2, G-CSF, Meg-CSF, thrombopoietin, stem cell factor, and erythropoietin. The pharmaceutical composition may further contain other agents which either enhance the activity of the protein or compliment its activity or use in treatment. Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with protein of the invention,  
25 or to minimize side effects. Conversely, protein of the present invention may be included in formulations of the particular cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent to minimize side effects of the cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent.

30 A protein of the present invention may be active in multimers (e.g., heterodimers or homodimers) or complexes with itself or other proteins. As a result, pharmaceutical compositions of the invention may comprise a protein of the invention in such multimeric or complexed form.

The pharmaceutical composition of the invention may be in the form of a complex of the protein(s) of present invention along with protein or peptide antigens. The protein and/or peptide antigen will deliver a stimulatory signal to both B and T lymphocytes. B lymphocytes will respond to antigen through their surface immunoglobulin receptor. T lymphocytes will respond to antigen through the T cell receptor (TCR) following presentation of the antigen by MHC proteins. MHC and structurally related proteins including those encoded by class I and class II MHC genes on host cells will serve to present the peptide antigen(s) to T lymphocytes. The antigen components could also be supplied as purified MHC-peptide complexes alone or with co-stimulatory molecules that can directly signal T cells. Alternatively antibodies able to bind surface immunoglobulin and other molecules on B cells as well as antibodies able to bind the TCR and other molecules on T cells can be combined with the pharmaceutical composition of the invention.

The pharmaceutical composition of the invention may be in the form of a liposome in which protein of the present invention is combined, in addition to other pharmaceutically acceptable carriers, with amphipathic agents such as lipids which exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers in aqueous solution. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids, and the like. Preparation of such liposomal formulations is within the level of skill in the art, as disclosed, for example, in U.S. Patent No. 4,235,871; U.S. Patent No. 4,501,728; U.S. Patent No. 4,837,028; and U.S. Patent No. 4,737,323, all of which are incorporated herein by reference.

As used herein, the term "therapeutically effective amount" means the total amount of each active component of the pharmaceutical composition or method that is sufficient to show a meaningful patient benefit, i.e., treatment, healing, prevention or amelioration of the relevant medical condition, or an increase in rate of treatment, healing, prevention or amelioration of such conditions. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

In practicing the method of treatment or use of the present invention, a therapeutically effective amount of protein of the present invention is administered to a mammal having a condition to be treated. Protein of the present invention may be

administered in accordance with the method of the invention either alone or in combination with other therapies such as treatments employing cytokines, lymphokines or other hematopoietic factors. When co-administered with one or more cytokines, lymphokines or other hematopoietic factors, protein of the present invention may be administered either simultaneously with the cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering protein of the present invention in combination with cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors.

Administration of protein of the present invention used in the pharmaceutical composition or to practice the method of the present invention can be carried out in a variety of conventional ways, such as oral ingestion, inhalation, topical application or cutaneous, subcutaneous, intraperitoneal, parenteral or intravenous injection. Intravenous administration to the patient is preferred.

When a therapeutically effective amount of protein of the present invention is administered orally, protein of the present invention will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the pharmaceutical composition of the invention may additionally contain a solid carrier such as a gelatin or an adjuvant. The tablet, capsule, and powder contain from about 5 to 95% protein of the present invention, and preferably from about 25 to 90% protein of the present invention. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean oil, or sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol. When administered in liquid form, the pharmaceutical composition contains from about 0.5 to 90% by weight of protein of the present invention, and preferably from about 1 to 50% protein of the present invention.

When a therapeutically effective amount of protein of the present invention is administered by intravenous, cutaneous or subcutaneous injection, protein of the present invention will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable protein solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred

pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection should contain, in addition to protein of the present invention, an isotonic vehicle such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicle as known in the art. The  
5 pharmaceutical composition of the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art.

The amount of protein of the present invention in the pharmaceutical composition of the present invention will depend upon the nature and severity of the condition being treated, and on the nature of prior treatments which the patient has undergone.  
10 Ultimately, the attending physician will decide the amount of protein of the present invention with which to treat each individual patient. Initially, the attending physician will administer low doses of protein of the present invention and observe the patient's response. Larger doses of protein of the present invention may be administered until the optimal therapeutic effect is obtained for the patient, and at that point the dosage is not  
15 increased further. It is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about 0.01  $\mu$ g to about 100 mg (preferably about 0.1mg to about 10 mg, more preferably about 0.1  $\mu$ g to about 1 mg) of protein of the present invention per kg body weight.

The duration of intravenous therapy using the pharmaceutical composition of the  
20 present invention will vary, depending on the severity of the disease being treated and the condition and potential idiosyncratic response of each individual patient. It is contemplated that the duration of each application of the protein of the present invention will be in the range of 12 to 24 hours of continuous intravenous administration. Ultimately the attending physician will decide on the appropriate duration of intravenous  
25 therapy using the pharmaceutical composition of the present invention.

Protein of the invention may also be used to immunize animals to obtain polyclonal and monoclonal antibodies which specifically react with the protein. Such antibodies may be obtained using either the entire protein or fragments thereof as an immunogen. The peptide immunogens additionally may contain a cysteine residue at the  
30 carboxyl terminus, and are conjugated to a hapten such as keyhole limpet hemocyanin (KLH). Methods for synthesizing such peptides are known in the art, for example, as in R.P. Merrifield, J. Amer.Chem.Soc. 85, 2149-2154 (1963); J.L. Krstenansky, *et al.*, FEBS Lett. 211, 10 (1987). Monoclonal antibodies binding to the protein of the invention may be useful diagnostic agents for the immunodetection of the protein. Neutralizing monoclonal

antibodies binding to the protein may also be useful therapeutics for both conditions associated with the protein and also in the treatment of some forms of cancer where abnormal expression of the protein is involved. In the case of cancerous cells or leukemic cells, neutralizing monoclonal antibodies against the protein may be useful in detecting and preventing the metastatic spread of the cancerous cells, which may be mediated by the protein.

For compositions of the present invention which are useful for bone, cartilage, tendon or ligament regeneration, the therapeutic method includes administering the composition topically, systematically, or locally as an implant or device. When administered, the therapeutic composition for use in this invention is, of course, in a pyrogen-free, physiologically acceptable form. Further, the composition may desirably be encapsulated or injected in a viscous form for delivery to the site of bone, cartilage or tissue damage. Topical administration may be suitable for wound healing and tissue repair. Therapeutically useful agents other than a protein of the invention which may also optionally be included in the composition as described above, may alternatively or additionally, be administered simultaneously or sequentially with the composition in the methods of the invention. Preferably for bone and/or cartilage formation, the composition would include a matrix capable of delivering the protein-containing composition to the site of bone and/or cartilage damage, providing a structure for the developing bone and cartilage and optimally capable of being resorbed into the body. Such matrices may be formed of materials presently in use for other implanted medical applications.

The choice of matrix material is based on biocompatibility, biodegradability, mechanical properties, cosmetic appearance and interface properties. The particular application of the compositions will define the appropriate formulation. Potential matrices for the compositions may be biodegradable and chemically defined calcium sulfate, tricalciumphosphate, hydroxyapatite, polylactic acid, polyglycolic acid and polyanhydrides. Other potential materials are biodegradable and biologically well-defined, such as bone or dermal collagen. Further matrices are comprised of pure proteins or extracellular matrix components. Other potential matrices are nonbiodegradable and chemically defined, such as sintered hydroxapatite, bioglass, aluminates, or other ceramics. Matrices may be comprised of combinations of any of the above mentioned types of material, such as polylactic acid and hydroxyapatite or collagen and tricalciumphosphate. The bioceramics may be altered in composition, such as in calcium-

aluminate-phosphate and processing to alter pore size, particle size, particle shape, and biodegradability.

Presently preferred is a 50:50 (mole weight) copolymer of lactic acid and glycolic acid in the form of porous particles having diameters ranging from 150 to 800 microns.

5 In some applications, it will be useful to utilize a sequestering agent, such as carboxymethyl cellulose or autologous blood clot, to prevent the protein compositions from disassociating from the matrix.

A preferred family of sequestering agents is cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), including methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and carboxymethylcellulose, the most preferred being cationic salts of carboxymethylcellulose (CMC). Other preferred sequestering agents include hyaluronic acid, sodium alginate, poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer and poly(vinyl alcohol). The amount of sequestering agent useful herein is 0.5-20

10 wt%, preferably 1-10 wt% based on total formulation weight, which represents the amount necessary to prevent desorption of the protein from the polymer matrix and to provide appropriate handling of the composition, yet not so much that the progenitor cells are prevented from infiltrating the matrix, thereby providing the protein the opportunity to assist the osteogenic activity of the progenitor cells.

20 In further compositions, proteins of the invention may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue in question. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF- $\alpha$  and TGF- $\beta$ ), and insulin-like growth factor (IGF).

25 The therapeutic compositions are also presently valuable for veterinary applications. Particularly domestic animals and thoroughbred horses, in addition to humans, are desired patients for such treatment with proteins of the present invention.

The dosage regimen of a protein-containing pharmaceutical composition to be used in tissue regeneration will be determined by the attending physician considering various factors which modify the action of the proteins, e.g., amount of tissue weight desired to be formed, the site of damage, the condition of the damaged tissue, the size of a wound, type of damaged tissue (e.g., bone), the patient's age, sex, and diet, the severity of any infection, time of administration and other clinical factors. The dosage may vary with the type of matrix used in the reconstitution and with inclusion of other proteins in

30



the pharmaceutical composition. For example, the addition of other known growth factors, such as IGF I (insulin like growth factor I), to the final composition, may also effect the dosage. Progress can be monitored by periodic assessment of tissue/bone growth and/or repair, for example, X-rays, histomorphometric determinations and tetracycline  
5 labeling.

Polynucleotides of the present invention can also be used for gene therapy. Such polynucleotides can be introduced either *in vivo* or *ex vivo* into cells for expression in a mammalian subject. Polynucleotides of the invention may also be administered by other known methods for introduction of nucleic acid into a cell or organism (including, without  
10 limitation, in the form of viral vectors or naked DNA).

Cells may also be cultured *ex vivo* in the presence of proteins of the present invention in order to proliferate or to produce a desired effect on or activity in such cells. Treated cells can then be introduced *in vivo* for therapeutic purposes.

15 Patent and literature references cited herein are incorporated by reference as if fully set forth.

## SEQUENCE LISTING

## (1) GENERAL INFORMATION:

- (i) APPLICANT: Jacobs, Kenneth  
McCoy, John M.  
LaVallie, Edward R.  
Racie, Lisa A.  
Merberg, David  
Treacy, Maurice  
Spaulding, Vikki  
Agostino, Michael J.
- (ii) TITLE OF INVENTION: SECRETED PROTEINS AND POLYNUCLEOTIDES  
ENCODING THEM
- (iii) NUMBER OF SEQUENCES: 30
- (iv) CORRESPONDENCE ADDRESS:
  - (A) ADDRESSEE: Genetics Institute, Inc.
  - (B) STREET: 87 CambridgePark Drive
  - (C) CITY: Cambridge
  - (D) STATE: MA
  - (E) COUNTRY: U.S.A.
  - (F) ZIP: 02140
- (v) COMPUTER READABLE FORM:
  - (A) MEDIUM TYPE: Floppy disk
  - (B) COMPUTER: IBM PC compatible
  - (C) OPERATING SYSTEM: PC-DOS/MS-DOS
  - (D) SOFTWARE: PatentIn Release #1.0, Version #1.30
- (vi) CURRENT APPLICATION DATA:
  - (A) APPLICATION NUMBER:
  - (B) FILING DATE:
  - (C) CLASSIFICATION:
- (viii) ATTORNEY/AGENT INFORMATION:
  - (A) NAME: Sprunger, Suzanne A.
  - (B) REGISTRATION NUMBER: 41,323
- (ix) TELECOMMUNICATION INFORMATION:
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  - (B) TELEFAX: (617) 876-5851

## (2) INFORMATION FOR SEQ ID NO:1:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 1551 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: double
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

GTGTTATTGT AGCGAGGGAC ATGAGCTGGA GGCTGATGGC ATCAGCTGCA GCCCTGCAGG	60
GGCCATGGGT GCCCAGGCTT CCCAGGACCT CGGAGATGAG TTGCTGGATG ACGGGGAGGA	120
TGAGGAAGAT GAAGACGAGG CCTGGAAGGC CTTC AACGGT GGCTGGACGG AGATGCCTGG	180
GATCCTGTGG ATGGAGCCTA CGCAGCCGCC TGA CTTTGCC CTGGCCTATA GACCGAGCTT	240
CCCAGAGGAC AGAGAGCCAC AGATACCCTA CCCGGAGCCC ACCTGGCCAC CCCCGCTCAG	300
TGCCCCCAGG GTCCCCCTACC ACTCCTCAGT GCTCTCCGTC ACCCGGCCTG TGGTGGTCTC	360
TGCCACGCGT CCCACACTGC CTCTGCCCCA CCAGCCTCCT GTGATCCCTG CCACACACCC	420
AGCTTTGTCC CGTGACCACC AGATCCCCGT GATCGCAGCC AACTATCCAG ATCTGCCTTC	480
TGCCTACCAA CCCGGTATTC TCTCTGTCTC TCATTCAGCA CAGCCTCCTG CCCACCAGCC	540
CCCTATGATC TCAACCAAAT ATCCGGAGCT CTTCCTGCC CACCAGTCCC CCATGTTTCC	600
AGACACCCGG GTCGCTGGCA CCCAGACCAC CACTCATTTG CCTGGAATCC CACCTAACCA	660
TGCCCCCTCTG GTCACCACCC TCGGTGCCCC GCTACCCCT CAAGCCCCAG ATGCCCTTGT	720
CCTCAGAACC CAGGCCACCC AGCTTCCCAT TATCCCACT GCCCAGCCCT CTCTGACCAC	780
CACCTCCAGG TCCCCTGTGT CTCCTGCCCC TCAAATCTCT GTGCCTGCTG CCACCCAGCC	840
CGCAGCCCTC CCCACCTCC TGCCCTCTCA GAGCCCCACT AACCAGACCT CACCCATCAG	900
CCCTACACAT CCCCATTTCA AAGCCCCCA AATCCCAAGG GAAGATGGCC CCAGTCCCAA	960
GTTGGCCCTG TGGCTGCCCT CACCAGCTCC CACAGCAGCC CCAACAGCCC TGGGGGAGGC	1020
TGGTCTTGCC GAGCACAGCC AGAGGGATGA CCGGTGGCTG CTGGTGCCAC TCCTGGTGCC	1080
AACCTGTGTC TTTTGTGGTG TCCTGCTTGC ACTGGGCATC GTGTACTGCA CCCGCTGTGG	1140
CCCCCATGCA CCAACAAGC GCATCACTGA CTGCTATCGC TGGGTATCC ATGCTGGGAG	1200
CAAGAGCCCC ACAGAACCCA TGCCCCCAG GGGCAGCCTC ACAGGGGTGC AGACCTGCAG	1260
AACCAGCGTG TGATGGGGTG CAGACCCCC TCATGGAGTA TGGGGCGCTG GACACATGGC	1320
CGGGGCTGCA CCAGGGACCC ATGGGGGCTG CCCAGCTGGA CAGATGGCTT CTGCTCCCC	1380
AGGCCCAGCC AGGGTCCTCT CTCAACCACT AGACTTGGCT CTCAGGAACCT CTGCTTCCTG	1440

GCCCAGCGCT CGTGACCAAG GATACACCAA AGCCCTTAAG ACCTCAGGGG GCGGGTGCTG 1500  
 GGGTCTTCTC CAATAAATGG GGTGTCAACC TTAAAAAAA AAAAAAAAAA A 1551

## (2) INFORMATION FOR SEQ ID NO:2:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 402 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Met	Gly	Ala	Gln	Ala	Ser	Gln	Asp	Leu	Gly	Asp	Glu	Leu	Leu	Asp	Asp	1	5	10	15
Gly	Glu	Asp	Glu	Glu	Asp	Glu	Asp	Glu	Ala	Trp	Lys	Ala	Phe	Asn	Gly	20	25	30	
Gly	Trp	Thr	Glu	Met	Pro	Gly	Ile	Leu	Trp	Met	Glu	Pro	Thr	Gln	Pro	35	40	45	
Pro	Asp	Phe	Ala	Leu	Ala	Tyr	Arg	Pro	Ser	Phe	Pro	Glu	Asp	Arg	Glu	50	55	60	
Pro	Gln	Ile	Pro	Tyr	Pro	Glu	Pro	Thr	Trp	Pro	Pro	Pro	Leu	Ser	Ala	65	70	75	80
Pro	Arg	Val	Pro	Tyr	His	Ser	Ser	Val	Leu	Ser	Val	Thr	Arg	Pro	Val	85	90	95	
Val	Val	Ser	Ala	Thr	Arg	Pro	Thr	Leu	Pro	Ser	Ala	His	Gln	Pro	Pro	100	105	110	
Val	Ile	Pro	Ala	Thr	His	Pro	Ala	Leu	Ser	Arg	Asp	His	Gln	Ile	Pro	115	120	125	
Val	Ile	Ala	Ala	Asn	Tyr	Pro	Asp	Leu	Pro	Ser	Ala	Tyr	Gln	Pro	Gly	130	135	140	
Ile	Leu	Ser	Val	Ser	His	Ser	Ala	Gln	Pro	Pro	Ala	His	Gln	Pro	Pro	145	150	155	160
Met	Ile	Ser	Thr	Lys	Tyr	Pro	Glu	Leu	Phe	Pro	Ala	His	Gln	Ser	Pro	165	170	175	
Met	Phe	Pro	Asp	Thr	Arg	Val	Ala	Gly	Thr	Gln	Thr	Thr	Thr	His	Leu	180	185	190	

Pro Gly Ile Pro Pro Asn His Ala Pro Leu Val Thr Thr Leu Gly Ala  
 195 200 205  
 Gln Leu Pro Pro Gln Ala Pro Asp Ala Leu Val Leu Arg Thr Gln Ala  
 210 215 220  
 Thr Gln Leu Pro Ile Ile Pro Thr Ala Gln Pro Ser Leu Thr Thr Thr  
 225 230 235 240  
 Ser Arg Ser Pro Val Ser Pro Ala His Gln Ile Ser Val Pro Ala Ala  
 245 250 255  
 Thr Gln Pro Ala Ala Leu Pro Thr Leu Leu Pro Ser Gln Ser Pro Thr  
 260 265 270  
 Asn Gln Thr Ser Pro Ile Ser Pro Thr His Pro His Ser Lys Ala Pro  
 275 280 285  
 Gln Ile Pro Arg Glu Asp Gly Pro Ser Pro Lys Leu Ala Leu Trp Leu  
 290 295 300  
 Pro Ser Pro Ala Pro Thr Ala Ala Pro Thr Ala Leu Gly Glu Ala Gly  
 305 310 315 320  
 Leu Ala Glu His Ser Gln Arg Asp Asp Arg Trp Leu Leu Val Ala Leu  
 325 330 335  
 Leu Val Pro Thr Cys Val Phe Leu Val Val Leu Leu Ala Leu Gly Ile  
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 Val Tyr Cys Thr Arg Cys Gly Pro His Ala Pro Asn Lys Arg Ile Thr  
 355 360 365  
 Asp Cys Tyr Arg Trp Val Ile His Ala Gly Ser Lys Ser Pro Thr Glu  
 370 375 380  
 Pro Met Pro Pro Arg Gly Ser Leu Thr Gly Val Gln Thr Cys Arg Thr  
 385 390 395 400  
 Ser Val

## (2) INFORMATION FOR SEQ ID NO:3:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2473 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

GGAGTATTGT GTCTACTTTT ATCTGTGCAC CAGCCACAAA TACCCACATT GGAAAGACCC	60
ATTGTGTATG GGTAAACATC CCTTCCTGTC TCCCACAACC CCTGTGACTG CCCTGCATGT	120
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CTGCCTCAGG ACCTCTGCTG AAGAGGGGGA TGAAGTGGGT CTCCAGGGAG GCAGTGGGGG	240
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ACACACCCCTT GTCCAAGGCT TTATGCATCG GATTTATTTT TCCAAATCAA GAGGACAGTG	420
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ACAGCTGGAA GGGTGCATGG CCCGCTCACC TTTGTTCAGA TGGGTGGAAA CGCTGATGAT	780
ACCAGTCTCT CCCTGCCGTG CCCCTGCCAC GGAGCAGGCA TTGTGAACTG GCTGGTGTTT	840
GCAGTCCCAC GTGGCATGGC CTCCAGCCCA ACCCAGAGTG GAGACTGGAG ACAGGGCAAT	900
GAGTCTGGTC GGGGGCACGT GGACATGCCC CATAGGGGCC CCACCCAGAC TTAACAGGCA	960
AGGTCTTGGG CATTCGCGA CGCAGGACTC AATGCTAAAG CAAGCCTGCC TGGCTCTGTG	1020
CCAGGGCCCC TCTTCTGATT TACACATCCC ATTTTACAC AGACCCTTCC TTCTTAATAA	1080
AGGCTGACAG TTCTGTTGGC AGCCAAGAAC CCACACCATG AAGACAGGGA GTGAGGGGCC	1140
TTTGTGCCCA ACTCCAGCAC AGCTGCGTTC TGGGTGTGT GAGAGGCATG TTCGTGTCTG	1200
TGCGCTGGTG GTCTCGTGAG ACAGTTCCGA GGACGGGAA ATTGCAGGGT GGTGGGGGCG	1260
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TGTATAATTG TTACGTGTAA TTTAAATAT ATCTGTTTGC CATCGTCATG AGAAGATTAT	1380
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CGAGTCATGA AATTGATGAC TGTGATCCA GTGGTGCAAG AAGCTACACT CCATGTGTCA	1500
TCACGCTTAT GACTCCTAAT GTATTTTAA GGCAAAAAAT GTCAGCCGAC TCCATCTTCA	1560
CCCCTCGATT CCTCGAGTCC AGCCTTTCTG TGCCAGTGCT TCACTGAGCC ACAACGCTCT	1620

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CGCCATCGGG ACCCGGCTGG GCCTGGAGTC TCGGGGCACA GTTGCCATGG AGCCCTCCTG 1680
GGTCATTCTA CAAATGTGCT GAGTGCCAGC TGA AAAACCCC ACAGGAGATG GAGTACCTTG 1740
GCCAAGCTTA AAGAGAAGAT TTTCTCAGGG TATTTATTAG TGTGTCCAGC AGGGTCAGGA 1800
AGCAGGATGG AAAGATGCAT TCAGACTGTT AATTTATTAA CAAGGCAAAAT GATTTTGTGT 1860
TTCTTGATGA CAGACTATTA AGTTTGGGAC TTATTTTCCC ATTTGAGAAG TTATAATATA 1920
TATTTAAGAT GATAAGTTTC CTGCTTAAGT TGTGCCTTTC AGCTTCAATG AGTTTAAGGA 1980
GCACTAAGGG TAATGATACC AATGAGGGTT GGT TTATTAT CAAACCTGAA TAGCTGTGGT 2040
TTCTCCAGTA AATATTTTCT TCTACTGAAC ATGGAGCCAT TATTAAGAGT TGTGTGTTTT 2100
TTATTATGTA CATTTGTATA TTTT TTGCT TGT TTGATGT TCTATTTTTC TAATAGTTTT 2160
CTTTTAGTTT CTAAAGTTG TGATACTAGA TTTAGATTCT GATGCTAACT GCAAATCAGG 2220
TTGGTCTCTG CTGGGTCTCT CCTGCTTTTA TTTTACTTTA AGGACAAGTG TAGTTGTCGT 2280
CCACCACCTT TCAAAAAATG TGAAACTGCC CTGCCTCCCC TTTT TGCTGA CAACACTGTG 2340
TACATTGACC ACTTCCTACC ATACTTTATG TTGTAAAATC AAACCTTTTT GTGGTACATT 2400
ATCTCATGCT TCTGCAAATT CGAATAAATT CTATGGCTTC CAAAAAAAAA AAAAAAAAAA 2460
AAAAAAAAAA AAA 2473

```

## (2) INFORMATION FOR SEQ ID NO:4:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 55 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

```

Val Ile Asp Ala Phe Ser Pro Gly Cys Leu Arg Lys Val Ala Lys Cys
1           5           10           15
Ile Leu Leu Ser Glu Leu Leu Arg Ser Pro Pro Thr Phe Gly Phe Cys
20          25          30
Ser Ser Lys Asn Ser Phe His Cys Asp Leu Phe Ser Leu Ser Gly Ser
35          40          45
Gln Pro Pro Gly Pro Leu Cys

```

50

55

## (2) INFORMATION FOR SEQ ID NO:5:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 4093 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

GCTAATTTTT TGTATTTTTA GTAGAGATGG GGTTCACCA CACTGGCCAG GCTTGTCTCG	60
CTCGAACTTC TGACCTCATG ATCCACCTGC CTCGGCCTCC CAAAGTGCTG GGATTACAGG	120
TGTGAGCCAC CGCACCTGGC AAAAGAGAAT CTTACAGAAC CTATTCAGTG GGAAGGAAGC	180
CCTCATTATA ATGATTTTCA TTCTTATGTG TGTTCAGGA CGACTGGGTT TGGATTCAGA	240
AGAGGATTAT TATACACCAC AAAAGGTGGA TGTTCCTAAG GCCTTGATTA TTGTGTCAGT	300
TCAATGTGGC TGTGATGGGA CATTTCTGTT GACCCAGTCA GGCAAAGTC TGGCCTGTGG	360
ACTCAATGAA TTCAATAAGC TGGGTCTGAA TCAGTGCATG TCGGGAATTA TCAACCATGA	420
AGCATACCAT GAAGTTCCTT ACACAACGTC CTTTACCTTG GCCAAACAGT TGTCTTTTAA	480
TAAGATCCGT ACCATTGCCC CAGGCAAGAC TCACACAGCT GCTATTGATG AGCGAGGCCG	540
GCTGCTGACC TTTGGCTGCA ACAAGTGTGG GCAGCTGGGC GTTGGGAAC TACAAGAAGCG	600
TCTGGGAATC AACCTGTTGG GGGGACCCCT TGGTGGGAAG CAAGTGATCA GGGTCTCCTG	660
CGGTGATGAG TTTACCATTG CTGCCACTGA TGATAATCAC ATTTTTCCTT GGGGCAATGG	720
TGGTAATGGC CGCCTGGCAA TGACCCCCAC AGAGAGACCA CATGGCTCTG ATATCTGTAC	780
CTCATGGCCT CGGCCTATTT TTGGATCTCT GCATCATGTC CCGGACCTGT CTGCGCTGG	840
ATGGCATACC ATTCTCATCG TTGAGAAAGT ATTGAATTCT AAGACCATCC GTTCCAATAG	900
CAGTGCTTAA TCCATTGGAA CTGTGTTTCA GAGCTCTAGC CCGGGAGGAG GCGGCGGGGG	960
CGGCGGTGGT GAAGAAGAGG ACAGTCAGCA GGAATCTGAA ACTCCTGACC CAAGTGAGG	1020
CTTCCGAGGA ACAATGGAAG CAGACCGAGG AATGGAAGGT TTAATCAGTC CCACAGAGGC	1080
CATGGGGAAC AGTAATGGGG CCAGCAGCTC CTGTCTGGC TGGCTTCGAA AGGAGCTGGA	1140



AAATGCAGAA TTTATCCCCA TGCCTGACAG CCCATCTCCT CTCAGTGCAG CGTTTTTCAGA	1200
ATCTGAGAAA GATACCCTGC CCTATGAAGA GCTGCAAGGA CTCAAAGTGG CCTCTGAAGC	1260
TCCTTTGGAA CACAAACCCC AAGTAGAAGC CTCGTCACCT CGGCTGAATC CTGCAGTAAC	1320
CTGTGCTGGG AAGGGAACAC CACTGACTCC TCCTGCCTGT GCGTGCAGCT CTCTGCAGGT	1380
GGAGTTGAG AGATTGCAGG GTCTGGTGTT AAAGTGTCTG GCTGAACAAC AGAAGCTACA	1440
GCAAGAAAAC CTCAGATTT TTACCEAACT GCAGAAGTTG AACAAAGAAAT TAGAAGGAGG	1500
GCAGCAGGTG GGAATGCATT CCAAAGGAAC TCAGACAGCA AAGGAAGAGA TGGAAATGGA	1560
TCCAAAGCCT GACTTCGATT CAGATTCCTG GTGCCTCCTG GGAACAAACT CCTGTAGACC	1620
CAGCCTCTAT TCTCCTGAGC CTATAGAGCC CCCAGGAGAC TGGGACCCAA AGAACTTCAC	1680
AGCACACTTA CCGAATGCAG AGAGCAGCTT TCCTGGCTTT GTTCACTTGC AGAAAAGGAG	1740
CGCAAGGCAG AGGCTCTGAA GCACTTTCCT TGTACATTTG GAGAGTGGA TTGCCTTTTA	1800
GATAGGATCT AGGAGTGATT TTATTGTTTT GGAGAATGGA AGGGCCCCCA TGGCCCTGGC	1860
TTTGTCACTA GTGACTGCCA TAGCAACAGC AGCTCTGTAC CTCATCTGTT GATCCCACCT	1920
TTGAAGAGGA GACACAGTGC TCACCTTAAT TGCGCTGGTA GCAGCTTATA TCCCATGTAT	1980
CATTTTCACC ATTGATTGGA AGCTGCCTTG GGAATTCAGT ACCAGGCATT ACCCCTCTGG	2040
GTGGGAGAGG GAGAAGTGTA AAGTTGGAGT GGGCTGGAAT CAGGTGTGGC CCGCCCAGTG	2100
TCCTCTGCAG AGTGGTGAAG TAGTCTGGCC CTCTTGGGAG CCCTGAGTCC AGGAAAATAT	2160
GTCTGATGGA GTCAATCTAG GGCTTGTTTC GAAAAAGTTC AGTTACTCTG TGCAGCTAAA	2220
TGCTTTAGGA GGAAAGGTAG GCTTAGGTTG CTTTCTCTCT GAGGGTTGAT TGAAATTTCT	2280
TCAGTGAGGA ATAGAGAAAG GGCAGGACCC TCATCATCAC ACAGCTGGTG TTTCAGGCTG	2340
TGACCAATGC AGGGTGGGAT TTCTTAACTG TGGATGAGGG GATGAGGTGT CTCTGAGGGA	2400
TGAGGTGTCT CAGAGAATTG AGTCCATGGG GCAGTCAGAA TAGCCTTAAG AGAAAAATCAT	2460
GAAGGAGAAG AGGTCTCTCT TTAGCTGCCT CTA CTGTTGTA TCTTAGAGAG GGCTTAGAGG	2520
GCTCTCAGTC TTCTGCCCAT GAAAAGACTT CTTTGAGCCT CTGCCTTCAT GGCTCTTAGG	2580
GTTCTGATCT TGATATCAGC AGCCCCAACC ACTTCTTTTC TGAATGTCTA GTCAGTATTT	2640
TTCCCTTTT GGTGTTTTAT GAAGCCATGT GGTAACGAAT GAATCTGTAT CATTTTTCTT	2700
ACCTGAGTGG CCCAAAGCCA GCACCAAACC CTGGGAGTCC CTGAAGCCTA ACAGAACAGG	2760
TAGA ACTTGC AAAAGGAATT TGGCTGAGAG CTCACTTCTA ATCCTGTACT CACTGTGTCT	2820

TTGTAGATAG AAACAAGCTA GCTTTACCAA AGAGAAATAG TGTCATAGAA GAACAAAAC	2880
TCATATAGAA AGTTCTAGGC AAGTATTTGA TGGTTTCCTT AAGGATGTGA GCTTTGTATT	2940
TCCACCTAGC CTTGTAAAAT GTTCCTGTGG TATTTTGTGT CACACATCCT ACCTTTGATG	3000
AGTCTCACAT CCCACCTTCC TATAAACAGC TAAATTAATT TTGTTTCATC TTCCCCAGAC	3060
CAAAATGTTT GATAATCTTA TCAACATTGT GGGAGGTCTT GTGCAATGGA AATTTTGCCA	3120
TTTCTCCAAA ACTGGTGGA TAAAGGCTGA TGCTTGGGA GAACCCCAT TCTCGGGACA	3180
GGCAACTCTG TTCAATGGGA TCTTCTTTGG TTTGATGTTT CCATGTGTTT CTCAGTTCTG	3240
GGAAGCCTAG TACATTAGTA CTAATGTAAT CACTGAAACC TTTCTTGAA ATAAGGAAG	3300
CAGCCAACT TTGATTAAAG TTGCAAGTTC TGGGGACTTG CGGGGGTGT CATAAAGT	3360
AACAGTGGGT TTTGGTTCAG CATGTAAATG CAACTTGAT TTTCTGAGG ACCGATTGAC	3420
CTGTATGTC CCTGTATCCT CATGCTCATC ATCTCAGCAG GCCTGAGAGG CTGGGTCAGT	3480
TTGGGTGTTT ATCATGAGGA TTGCTTCTGC CATGGAGCTG ATGGACGTGG GCAGGTGCT	3540
GAGAAGGTGG GGTGAAAGTG AGTGCCGGGG GTGGGTGAGT GCCCTGGTCT TGTTCATAGG	3600
GGAGCCTTTC CCTAGCAGTG GAACGCTGTG GTCATTTTCT CTAGCATATT CCCTTGGGAA	3660
GTCTAGATTT GCTATTAATC TGGCTGAGAA TCTAAGTTCT GTGCCCTAGA GACAGTTTGC	3720
ACTTTCCCAT ATTGTGCCTG GGACAGCCAT ATGATTTTTT TTTCCACCAA ACAAGTATGC	3780
<del>AAACAGAAAC CAGTTTCAAA GGGGGATGGA CTAAAAGATG AGGCAGTAGA AATGGGTTTG</del>	<del>3840</del>
AATGGTTTTT CTGTAGCTAA TTCTCTTTAA ATTTGTCCT GCTTTTTTTC TTTATGCAGT	3900
GCTAGGTGTT TTAAGTTTTT TAGTAGTATT GCTTTTGAGT TACAGTATAA CCTGAGTTAC	3960
TCCTCTGCTC TAACATTGTT GCAGAAGAGT AACTCAGGTT ATTGTTAGCC AGGTTGCTTG	4020
AAAGGTGAG AGTGGAGTGG TTTGGCATT TGTGTTTTAA TAAACATTTA AGCTCTTAAA	4080
AAAAAAAAA AAA	4093

## (2) INFORMATION FOR SEQ ID NO:6:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 522 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Met Ile Phe Ile Leu Met Cys Val Ser Gly Arg Leu Gly Leu Asp Ser  
 1 5 10 15  
 Glu Glu Asp Tyr Tyr Thr Pro Gln Lys Val Asp Val Pro Lys Ala Leu  
 20 25 30  
 Ile Ile Val Ala Val Gln Cys Gly Cys Asp Gly Thr Phe Leu Leu Thr  
 35 40 45  
 Gln Ser Gly Lys Val Leu Ala Cys Gly Leu Asn Glu Phe Asn Lys Leu  
 50 55 60  
 Gly Leu Asn Gln Cys Met Ser Gly Ile Ile Asn His Glu Ala Tyr His  
 65 70 75 80  
 Glu Val Pro Tyr Thr Thr Ser Phe Thr Leu Ala Lys Gln Leu Ser Phe  
 85 90 95  
 Tyr Lys Ile Arg Thr Ile Ala Pro Gly Lys Thr His Thr Ala Ala Ile  
 100 105 110  
 Asp Glu Arg Gly Arg Leu Leu Thr Phe Gly Cys Asn Lys Cys Gly Gln  
 115 120 125  
 Leu Gly Val Gly Asn Tyr Lys Lys Arg Leu Gly Ile Asn Leu Leu Gly  
 130 135 140  
 Gly Pro Leu Gly Gly Lys Gln Val Ile Arg Val Ser Cys Gly Asp Glu  
 145 150 155 160  
 Phe Thr Ile Ala Ala Thr Asp Asp Asn His Ile Phe Ala Trp Gly Asn  
 165 170 175  
 Gly Gly Asn Gly Arg Leu Ala Met Thr Pro Thr Glu Arg Pro His Gly  
 180 185 190  
 Ser Asp Ile Cys Thr Ser Trp Pro Arg Pro Ile Phe Gly Ser Leu His  
 195 200 205  
 His Val Pro Asp Leu Ser Cys Arg Gly Trp His Thr Ile Leu Ile Val  
 210 215 220  
 Glu Lys Val Leu Asn Ser Lys Thr Ile Arg Ser Asn Ser Ser Gly Leu  
 225 230 235 240  
 Ser Ile Gly Thr Val Phe Gln Ser Ser Ser Pro Gly Gly Gly Gly Gly  
 245 250 255  
 Gly Gly Gly Gly Glu Glu Glu Asp Ser Gln Gln Glu Ser Glu Thr Pro  
 260 265 270  
 Asp Pro Ser Gly Gly Phe Arg Gly Thr Met Glu Ala Asp Arg Gly Met

275	280	285
Glu Gly Leu Ile Ser Pro Thr	Glu Ala Met Gly Asn Ser Asn Gly Ala	
290	295	300
Ser Ser Ser Cys Pro Gly Trp Leu Arg Lys Glu Leu Glu Asn Ala Glu		
305	310	315
Phe Ile Pro Met Pro Asp Ser Pro Ser Pro Leu Ser Ala Ala Phe Ser		
325	330	335
Glu Ser Glu Lys Asp Thr Leu Pro Tyr Glu Glu Leu Gln Gly Leu Lys		
340	345	350
Val Ala Ser Glu Ala Pro Leu Glu His Lys Pro Gln Val Glu Ala Ser		
355	360	365
Ser Pro Arg Leu Asn Pro Ala Val Thr Cys Ala Gly Lys Gly Thr Pro		
370	375	380
Leu Thr Pro Pro Ala Cys Ala Cys Ser Ser Leu Gln Val Glu Val Glu		
385	390	395
Arg Leu Gln Gly Leu Val Leu Lys Cys Leu Ala Glu Gln Gln Lys Leu		
405	410	415
Gln Gln Glu Asn Leu Gln Ile Phe Thr Gln Leu Gln Lys Leu Asn Lys		
420	425	430
Lys Leu Glu Gly Gly Gln Gln Val Gly Met His Ser Lys Gly Thr Gln		
435	440	445
<del>Thr Ala Lys Glu Glu Met Glu Met Asp Pro Lys Pro Asp Phe Asp Ser</del>		
<del>450</del>	<del>455</del>	<del>460</del>
Asp Ser Trp Cys Leu Leu Gly Thr Asn Ser Cys Arg Pro Ser Leu Tyr		
465	470	475
Ser Pro Glu Pro Ile Glu Pro Pro Gly Asp Trp Asp Pro Lys Asn Phe		
485	490	495
Thr Ala His Leu Pro Asn Ala Glu Ser Ser Phe Pro Gly Phe Val His		
500	505	510
Leu Gln Lys Arg Ser Ala Arg Gln Arg Leu		
515	520	

## (2) INFORMATION FOR SEQ ID NO:7:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 1601 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: double
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

CCCACGAGG CCTTCGACCA TGAGGTCTCC GCCTTCTTCC CCGCCAACCT GGACTTCCTG	60
TGCTGCAGG AGGTGTTTGA CAAGCGAGCA GCCACCAAAT TGAAAGAGCA GCTGCACGGC	120
TACTTCGAGT ACATCCTGTA CGACGTCGGG GTCTACGGCT GCCAGGGCTG CTGCAGCTTC	180
AAGTGTCTCA ACAGCGGCCT CCTCTTTGCC AGCCGCTACC CCATCATGGA CGTGGCCTAT	240
CACTGTTACC CCAACAAGTG TWACKACSAT GCCCTGGCCT CTAAGGGAGC TCTGTTTCTC	300
AAGGTGCAGG TGGGAAGCAC ACCTCAGGAM CAAARAATCG TCGGGTACAT CGCCTGCACA	360
CACCTGCATG CCCCACAAGA GGACAGCGCC ATCCGGTGTG GGCAGCTGGA CCTGCTTCAG	420
GACTGGCTGG CTGATTTCGG AAAATCTACC TCCTCGTCCA GCGCAGCCAA CCCCAGGAG	480
CTGGTGGCAT TTGACGTCGT CTGTGGAGAT TTCAACTTTG ATAAGTCTC CTCTGACGAC	540
AAGCTGGAGC AGCAACACTC CCTGTTTACC CACTACAGGG ACCCTGCCG CCTGGGGCCT	600
GGTGAGGAGA AGCCGTGGGC CATCGTACT CTGCTGGACA CGAACGGCCT GTACGATGAG	660
GATGTGTGCA CCCCCGACAA CCTGCAGAAG GTCTTGGAGA GTGAGGAGGG CCGCAGGGAG	720
TACCTGGCGT TTCCACCAG CAAGAGCTCG GGCCAGAAGG GGCGGAAGGA GCTGCTGAAG	780
GGCAACGGCC GGCGCATCGA CTACATGCTG CATGCAGAGG AGGGGCTGTG CCCAGACTGG	840
AAGGCCGAGG TGGAAGAATT CAGTTTATC ACCCAGCTGT CCGGCCTGAC GGACCACYTG	900
CCAGTAGCCA TGCGACTGAT GGTGTCTTCG GGGGAGGAGG AGGCATAGAC CGTCCGGAGC	960
AGCGGGGCTT CTGCCAGCCC TTGCAGCTGC AGCCCATCCC TGGGCCATGT CCCCTCCATC	1020
GAGTGCCCGG TGCTTGGGGG AGGAGGCGAG GGACAGGGAG GGAGCCACAG TCAGTGCCCG	1080
GGAACTGGA AGCTGCGCTG CTCTGCGCCT CTGGGCCTCA CTGTGGSCAG AGGAGTCAGG	1140
CCCGCCCCAG GAGCTCCAG CTGCCTAACC AGTGCCATTC TTTCACAACA CGATTTTCTA	1200
CAAACTTACA GCACAACCGA GTTTGTAACC CGTGGGTTAG TATGAGGACC GGGTTCGTGT	1260
ACTCTCTGTA TCTCTCTTA AGCTTCGTCC AGGGTTCTTT ATTTTGTCT GCTGCCAATG	1320
TCGTCTCGCA TGCCTGCACC CTCGCATGCA CGCTGCCCCG ATGCCACGTG CCACGCTGTA	1380
GCCACAGACC CCTTGCTCGG GCCTCACCCA AGGCCAAACT CCAAACACAA TCAGAACCAG	1440

CCAAAGAAGC ACTTCCTGGG CACGGCCACC AGCTCTCCCG CCTCCAGTGT GGGCCGGCTC 1500  
 CTGCAGGGTC CGAGGGCTGC ATCTCTACCA GCCAGCCCAG GGCTCTTCCC AGGGTCTCGC 1560  
 ATTCAAGGGC AATTACATTT TAAAAAAAAA AAAAAAAAAA A 1601

## (2) INFORMATION FOR SEQ ID NO:8:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 240 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Met Asp Val Ala Tyr His Cys Tyr Pro Asn Lys Cys Xaa Xaa Xaa Ala  
 1 5 10 15  
 Leu Ala Ser Lys Gly Ala Leu Phe Leu Lys Val Gln Val Gly Ser Thr  
 20 25 30  
 Pro Gln Xaa Gln Xaa Ile Val Gly Tyr Ile Ala Cys Thr His Leu His  
 35 40 45  
 Ala Pro Gln Glu Asp Ser Ala Ile Arg Cys Gly Gln Leu Asp Leu Leu  
 50 55 60  
 Gln Asp Trp Leu Ala Asp Phe Arg Lys Ser Thr Ser Ser Ser Ala  
 65 70 75 80  
 Ala Asn Pro Glu Glu Leu Val Ala Phe Asp Val Val Cys Gly Asp Phe  
 85 90 95  
 Asn Phe Asp Asn Cys Ser Ser Asp Asp Lys Leu Glu Gln Gln His Ser  
 100 105 110  
 Leu Phe Thr His Tyr Arg Asp Pro Cys Arg Leu Gly Pro Gly Glu Glu  
 115 120 125  
 Lys Pro Trp Ala Ile Gly Thr Leu Leu Asp Thr Asn Gly Leu Tyr Asp  
 130 135 140  
 Glu Asp Val Cys Thr Pro Asp Asn Leu Gln Lys Val Leu Glu Ser Glu  
 145 150 155 160  
 Glu Gly Arg Arg Glu Tyr Leu Ala Phe Pro Thr Ser Lys Ser Ser Gly  
 165 170 175  
 Gln Lys Gly Arg Lys Glu Leu Leu Lys Gly Asn Gly Arg Arg Ile Asp

	180		185		190
Tyr Met Leu His Ala Glu Glu Gly Leu Cys Pro Asp Trp Lys Ala Glu					
195		200		205	
Val Glu Glu Phe Ser Phe Ile Thr Gln Leu Ser Gly Leu Thr Asp His					
210		215		220	
Leu Pro Val Ala Met Arg Leu Met Val Ser Ser Gly Glu Glu Glu Ala					
225		230		235	240

## (2) INFORMATION FOR SEQ ID NO:9:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2274 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

GGCGTTGCTG GTGCGAGTCC TTAGGAACCA GACTAGCATT TCTCAGTGGG TTCCAGTATG	60
CAGCCGATTG ATACCTGTGT CTCCTACCCA AGGACAGGGG GACAGGGCTC TGTCTCGCAC	120
TTCCCAGTGG CCCAGATGA GCCAGTCCCA AGCATGTGGT GGATCAGAAC AGATTCTCTGG	180
AATAGACATA CAGCTGAATA GGAAGTATCA CACCACACGT AAGCTTTCTA CTACCAAAGA	240
TTCCCCACAG CCTGTTGAGG AGAAGGTTGG TGCTTTCACA AAGATAATAS AAGCCATGGG	300
ATTACCGGGA CCTTTGAAAT ACAGTAAATG GAAGATTAAG ATTGCGGCCC TGCGCATGTW	360
TACTAGCTGT GTGGAGAAAA CTGACTTCGA GGAATTCTTT CTAAGGTGTC AGATGCCTGA	420
TACATTCAAT TCATGGTTTC TTATAACCCT ACTCCACGTC TGGATGTGTC TAGTCCGAAT	480
GAAGCAGGAA GGCCGGAGTG GGAAGTACAT GTGTCGTATC ATAGTTTCATT TTATGTGGGA	540
GGATGTTTCA CAGCGCGGCA GAGTCATGGG GGTTAATCCC TATATCCTGA AGAAGAACAT	600
GATCCTCATG ACAAATCATT TCATATGCAGC GATCTTGGA TATGATGAGG GGATCCTTTC	660
AGATGATCAT GGGCTGGCCG CTGCCCTCTG GAGAACCTTC TTCAACCGGA AATGTGAAGA	720
CCCTCGACAT CTTGAATTGC TGGTAGAGTA TGTGAGGAAA CAGATACAGT ACCTGGACTC	780
CATGAACGGG GAGGATCTGC TTCTGACAGG GGAGGTGAGC TGGCGCCCTC TAGTGGAGAA	840

GAATCCTCAG AGCATCCTGA AGCCCCATTC TCCGACTTAC AACGACGAGG GACTTTGATG	900
GGCTGGGCCC TCCGCACGGC CCGCCAGCTG GCTTCGAGGA ACCTCCAGGA GAGAAGTGCC	960
TGTTGGTCCA GGACCCTGCA GAAAGTGGCC TGAAGTGACC TCTGAACAGC ATCTGTCAAA	1020
TACCTGGCCC CATTGTGTGT GAGTTTCCTC TTAGTGTGCC CAGGAGTCTG ATCTGTGGG	1080
GTACAGGGCT GGGAGAACCC CTAGCTCTCC CGGGGTGTCC TCTCCCTTAG GGAAGCCCC	1140
GAGTGAGAGT CCCCCAGCAC AACTCCCCA ACCCCCTCCA GCAACTACAT GTGACTGATA	1200
GCTTTTCCCA AAGGCCAAGG AAGGGATGGT GTAGGTCAA AAGGGAACC CCCCAGGGCC	1260
TGCTGTGGCC TAGGAGCAGA TTGTAATGCT GCCGAGTCCG GTCGGTGACC ACGCGTTGTC	1320
CCTCGGCTTT CAGCCATGGG GTTGAGTTGG CCATTAAAAG AAACAGAGAC TTCTCTCTGC	1380
CATGGCCCTT CTTTATTCCA GGGACTTAGA AACTTGCCTG AGATGGTGGA CGCAGTAATG	1440
AGGGCACCGC GCAGCTCAGT TAGAGACGGA GAAAGGAAG AGGCTGGGAT GGTCTCTGCT	1500
GCTCTTGCTT CTAGTTCATG GAGATGTGTC TCTGTTCAGG CCAAGATACA GCCAGCCAGG	1560
CCTGTGCTCT GGGACCCAGG AGGCCTCTGA TGACCAAGGG CTTTCACATC CTAAGTCATT	1620
TGGAAGGAGG CTTGAGAAC AAAGTCACCT TTGTCACTCC CAGTGAAGT AATGAGGAAC	1680
ATGCTGTCTC CTGTCTTGGC CTCCCCTTTC ATGAGATACT GGGGAGAAGA GAACATTCCT	1740
CCTGGCTTAG TTGTAGCAGA CCCAGACCTG TGCCAGCTT TGGTCCCCCT TCCCAACTTC	1800
TGAAGCACGT GCTGCAGAGC CACCTTGGTC TGAGCACCTG AGGACCAGCC CCTCCTCCCT	1860
CAGTGCGGGT CATCTCTTGG GGGATTTTCT TAAAGTGAAG AAAGGGGGTG GGAACCATA	1920
TGCCCCCTCC CTCCCCATC AAATTCCTT CATTTAACTT GCTATAAAAT GAGTCATATA	1980
AAGAAACTCT ATATGGGTGA GGTATATCCC ACTTCTGTGA AAACATTACA AATCAAACCG	2040
CTTCTCTCAG TTATTTAAG ATGCTTTTGT TGCGAGCGGA GCTCTAGAGT GAAGCCTCCT	2100
GTGTGTGTGT GAGATAATAA CACCTTGTA CTCATTACAG CTGGGCACTA TTACATAAA	2160
CCAGAGCTGA GCCAGGCAGG AATTGCTGA TTAATTTATT TTTAATGGAG TGAAGTATAC	2220
CATGCACCAA AATAAACTTT ACTGTGTGTA CCTAAAAAAA AAAAAAAAAA AAAA	2274

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 253 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear



(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

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Met Ser Gln Ser Gln Ala Cys Gly Gly Ser Glu Gln Ile Pro Gly Ile
1           5           10           15
Asp Ile Gln Leu Asn Arg Lys Tyr His Thr Thr Arg Lys Leu Ser Thr
20           25           30
Thr Lys Asp Ser Pro Gln Pro Val Glu Glu Lys Val Gly Ala Phe Thr
35           40           45
Lys Ile Ile Xaa Ala Met Gly Phe Thr Gly Pro Leu Lys Tyr Ser Lys
50           55           60
Trp Lys Ile Lys Ile Ala Ala Leu Arg Met Xaa Thr Ser Cys Val Glu
65           70           75           80
Lys Thr Asp Phe Glu Glu Phe Phe Leu Arg Cys Gln Met Pro Asp Thr
85           90           95
Phe Asn Ser Trp Phe Leu Ile Thr Leu Leu His Val Trp Met Cys Leu
100          105          110
Val Arg Met Lys Gln Glu Gly Arg Ser Gly Lys Tyr Met Cys Arg Ile
115          120          125
Ile Val His Phe Met Trp Glu Asp Val Gln Gln Arg Gly Arg Val Met
130          135          140
Gly Val Asn Pro Tyr Ile Leu Lys Lys Asn Met Ile Leu Met Thr Asn
145          150          155          160
His Phe Tyr Ala Ala Ile Leu Gly Tyr Asp Glu Gly Ile Leu Ser Asp
165          170          175
Asp His Gly Leu Ala Ala Ala Leu Trp Arg Thr Phe Phe Asn Arg Lys
180          185          190
Cys Glu Asp Pro Arg His Leu Glu Leu Leu Val Glu Tyr Val Arg Lys
195          200          205
Gln Ile Gln Tyr Leu Asp Ser Met Asn Gly Glu Asp Leu Leu Leu Thr
210          215          220
Gly Glu Val Ser Trp Arg Pro Leu Val Glu Lys Asn Pro Gln Ser Ile
225          230          235          240
Leu Lys Pro His Ser Pro Thr Tyr Asn Asp Glu Gly Leu
245          250

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## (2) INFORMATION FOR SEQ ID NO:11:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2711 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

TATCCATTAC GTCGACTAAT ACGTACATAA GAATTCAATC GGGCCTTGGG GCTGGCCCTG	60
AAACCTGCGA GGGGCTTCCG TCCACGTCCC CAGTGGACCT ACCACCCCTC CATCTGGGAA	120
AGCAGGCCAC AGCAGCCGGA CAAAGGAAGC TCCTCAGCCT CTAGTCGCCT CTCTGTGCAT	180
GCACATCGGT CACTGATCTC GCCTACTGGC ACAGACGTGT TTATCGGCCA ACCTGACCCCT	240
CACAAAAAGC TACCACCGAA GTGGACAGGC CCCTACACTG TGATACTCAG CACACCAACT	300
GCAGTGAGAG TCCGAGGACT CCCCAACTGG ATCCATCGCA CCAGGGTCAA GCTCACCCCC	360
AAGGCAGCTT CTTCTCCAA AACATTAACA GCTAAGTGT TGTCTGGGCC AATTCTCCT	420
ACCAAGTTTA AATTAACCAA CATTTTTC TTAACCAA AACACAAGGA AGACTAACCA	480
CGTGCTTCCA GGAATGGCCT GTATCTACCC AACCATTTC TATACCTCTC TTCCAACCAA	540
AAGTCTTAAT ATGGGAATAT CCCTCACCAC GATCCTAATA CTGTCAGTAG CTGTCCTGCT	600
GTCCACAGCA GCCCTCCGA GCTGCCGTA GTGTTATCAG TCTTTGCACT ACAGAGGGGA	660
GATGCAACAA TACTTTACTT ACCATACTCA TATAGAAAGA TCCTGTTATG GAACTTAAT	720
CGAGGAATGT GTTGAATCAG GAAAGAGTTA TTATAAGTA AAGAATCTAG GAGTATGTGG	780
CAGTCGTAAT GGGGCTATTT GCCCCAGAGG GAAGCAGTGG CTTTGCTTCA CCAAAATGG	840
ACAATGGGGA GTAAACACTC AGGTGCTTGA GGACATAAAG AGAGAACAGA TTATAGCCAA	900
AGCCAAAGCC TCAAAACCAA CAACTCCCC TGAAAATCGC CCGCGGCATT TCCATTCTCT	960
TATACAAAA CTATAAGCAG ATGCATCCCT TCCTAAGCCA GGAAAAATC TGTTGTGTA	1020
TCTAGGAGAA CCATGTGCT TACCATGAAT GTGTCCAATT GTTGGGTATG CGGGGGAGCT	1080
TTATGAGTGA ACAGTGGCTG TGGGACGGGA TAGACATTCC CCCTTACTTA CAGGCATCCC	1140
AAAACCCAG ACTCACTTTC ACTCCTCAGG AATGCCCGCA GTCCTGGACA CTTACCAACT	1200

CAGTATGAGG GACGGTGTGC ATATCCCGCA AGTGGACTGA TAAAACCCAT CGCGCCGTAG	1260
GTGAAAACCC GTCACCAAAC CCTAACAGTC AATGCCTCCA TAGCTGAGTG GTGGCCAAGG	1320
TTACCCCTCG GAGCCTGGTC TCCTTCTAAC TTAAGCTACC TCAATTGTGT CTTGTCAAAA	1380
AAGGCCTGGT ACTGTACAAA CACCACTAAC CCTTATGCCG CATACCTCCG CCTAAGTGTA	1440
CTATGCGACA ATCCTAGGAA CACCAGCTGA CAATGGACTG CCACTGACGG ATTCTGTGG	1500
ATATGGGGAA CCCAGGCTTA CTCACAGCTA CCTTATCACT GGCAAGGTAC TTGCTTCCTA	1560
GGCACAATTC AACCTGGATT CTTTTTACTT CCGAAGCAGC CGGGCAACAC CCTCAGAGTC	1620
CCTGTGTATG ATAACCAGAG AAAAAATGATC CTTGGAGGTA GGAGGGAGCC AAAGATTGTG	1680
AGAGGACGAG TGGCCTCCGC AACGGATCAT TGAATACTAT GGTCTGCCA CTTGGGCAGA	1740
GGATGGTTCA TGGGGTATC GCACTCCCAT ATATATGCCA AATAGAGCGA TTAGACTACA	1800
AGCTGTTCTA GAGATAATCA CTAACCAAAC TGCCTCAGCC CTAGAAATGC TCGCGCAACA	1860
ACAAAACCAA ATGCGCGCGG CAATTTATCA AAACAGGCTG GCCCTAGACT ACTTATTAGC	1920
AGAAGAGGGT GCGGGCTGTG GTAAGTTTAA CATCTCCAAT TGCTGTCTTA ACATAGGCAA	1980
TAATGGAGAA GAGGTCTTGG AAATCGCTTC AAACATCAGA AAAGTAGCCC GTGTACCAGT	2040
CCAAACCTGG GAGGGATGGG ACCCAGCAAA CTCTAGGAG GGTGGTTCTC TAATTTAGGA	2100
GGATTTAAAA TGCTGGTGGG GACAGTCATT TTCATCACTG GGTCTCTCCT GTTCTCCTCC	2160
TGTGGTATCC CATTAAAACT CTTGTTGAAA CTACAGTTAA CCTCCTGACA ATCCAGATGA	2220
TGCTCCTGCT ACAGCGGCAC GATGGATACC AACCCGTCTC TCAAGAATAC CCAAAAAATT	2280
AAGTTTTTCT TTTTCCAAGG TGCCACGCC ACCCYTATGT CACGCCTGAA GTAGTTATTG	2340
AGAAAGTCGT CCCTTTCCTC TTTTCTATAA CCAAATAGAC AGGAATGGAA GATTCTCCTC	2400
GGGGCCTGAA AGCTTGCGGG ATGAATAACT CCTCCTCCTC AGGCCAGTC CCAAGGTACA	2460
AACTTGCACC AGCAGCAAGA TAGCAGAGGC AGGAAGAGAG CTGGCTGGAA GACACGTACC	2520
CCCTGAAGAT CAAGAGGGAG GTCGCCCTGG TACTACATAG CAGTCACGTT AGGCTGGGAC	2580
AATTCCTGTT TACAGAGGAC TATAAAACCC CTGCCCCATC CTCACTTGGG GCTGATGCCA	2640
TTTTAGGCCT CAGCCTGTCT GCATGCAGGC GCTCATTAAC ACAGCATGTT GCTCCAAAAA	2700
AAAAAAAAA A	2711

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 160 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

```

Met Ala Cys Ile Tyr Pro Thr Thr Phe Tyr Thr Ser Leu Pro Thr Lys
 1           5           10           15
Ser Leu Asn Met Gly Ile Ser Leu Thr Thr Ile Leu Ile Leu Ser Val
          20           25           30
Ala Val Leu Leu Ser Thr Ala Ala Pro Pro Ser Cys Arg Glu Cys Tyr
          35           40           45
Gln Ser Leu His Tyr Arg Gly Glu Met Gln Gln Tyr Phe Thr Tyr His
 50           55           60
Thr His Ile Glu Arg Ser Cys Tyr Gly Asn Leu Ile Glu Glu Cys Val
 65           70           75           80
Glu Ser Gly Lys Ser Tyr Tyr Lys Val Lys Asn Leu Gly Val Cys Gly
          85           90           95
Ser Arg Asn Gly Ala Ile Cys Pro Arg Gly Lys Gln Trp Leu Cys Phe
          100          105          110
Thr Lys Ile Gly Gln Trp Gly Val Asn Thr Gln Val Leu Glu Asp Ile
          115          120          125
Lys Arg Glu Gln Ile Ile Ala Lys Ala Lys Ala Ser Lys Pro Thr Thr
          130          135          140
Pro Pro Glu Asn Arg Pro Arg His Phe His Ser Phe Ile Gln Lys Leu
          145          150          155          160

```

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2892 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

TGATTATTGA GCATAACTGA TGAGAGAATG ACAGTATTGG TGACTAGCTT TTTTGT'TTTT	60
AAATAACACA CTTTAAATG CCACAGTGTT ATTTGAAAGC TTAAAGGCAT TTTCTCATCT	120
TCAGTATTTG CTTTTTATCA GTTGTAGAAA AGAACCTTAG TG'TTTTCTTC TCTACCTATG	180
TATGCTTATG AAACCGCTCT ACCTACATAT GAAACTTCTC TACCTATGTA TG'TTTACGAA	240
AAGAGATGTA TTTGCCAAGA AAATCTTGAT TATATAAAAG AAAAAAGAT TATAAAAGAC	300
AGTTTCTGTT TAAGTAAAC TGTCTTTGAA ACTTAAGAAA GCTTAAGTTT TAAAAAATC	360
TCAGTTAAAC ATCATTGGTT TATTGACTT ACTGTAACT CTTGCTTCTC TTTGACTCCA	420
TGGTGT'TTTT AGATAACCAT GTATGAACCT TATGTTAATG GTTTGTGGGA TACTAAAATA	480
GCTTGAAGAT GACTTGATGA CTGTGCATTT TATATAGTTT TATTCTCCTA AAATCTCAGG	540
AGGGCAGCAA GTGCTGTCAA CGATTATATA GTGATGAGAT TTTTATGGGA ATGATT'TCTT	600
CTTGGTGCGT TTTACACATT TGTACTGATA GCAAACTAA AGTTTAAAGC AGCAAAGTTT	660
AAGTTCTCCT TAAATCCTAC AGAAACCAAC CTTTAAAGGA CATAATTTCA TCTAAACAT	720
GACGATATTT AGCACACCTT TTAATGTGGG TATATATCAA GTGTTTAAAG ACTGGCTAGT	780
ATGTGATAGA GCAAGACCTG AGACTTTATA AGTATTTGCT CGTGTCTGTT GACAGACCTC	840
TTTCTTTCAA ACTTGTTAGA AGAGTGGTAA GACATATCCA ATTGGAAAAT AAGATGCAGT	900
GTGTATATAG ACATACATTT AAAGTGCTTG CGTTAAATTT AGTTTCTCAA TAAGATAAAA	960
TTATTTTAAA AATTGGTTC ACTTTATTAC AATAGTGGCA ATTTAGCTTT TCAGTATTAC	1020
AGGAATTTAA AAATGGTTT CTGTAGGGG ACATCTCAAC TTTGGGAATA TCTTCACTTA	1080
ATTTTAAAAA AATATTTTCA TGCTTTATG TCCAGCTATA CAATATATCG CAAAATCCTG	1140
ACAAGTTCAT TGTATTAAGG TATTAACAT TACATGGAAA GCAATTCTGT TCATCTTTTG	1200
ATGTTTGTGT TGAAAATGCT TATCTTTGTG TTTTGATCTT CCAACAGCTG AGAGCTTGAA	1260
CTGATTTAAA CATTTGTCAA TACTTTAAG AATGCTTTAA GTAAAGAAGG GGAAAATTTT	1320
AAGTAAGTTT TTTCCCTTCT AGGAAGAAAA ACTATGATGA TGTTAAGAAA ATGTCATTAT	1380
AGAGCTTGCT CAATAATATG TTCTTTAAAT CCACCTCCAT TTGTACATTA TAGGTATCAT	1440
TCTGTTTTTG CTAAAAATA TCTGCAACCA TTTCAGATAG TTTTACAGCA AATTGATCTA	1500
AAAGCCACTA ATAAATCTA GGGTTTGAGT CTAGAAGCCA AGCAAAGTGT CACCAATGTC	1560
AGTTGTAAAT TAGAATGCAA CATGAGGCTT CAGACTCATG ACAATGATAT ACATGAAAAAC	1620

AAAAATATAA TTGTGTCTAC CTTCTACTT TCCCTTTTGA CATATGTAGT TGGAATTTTA	1680
CATAGTCTTA AAATCCATAT TTAGAATCTT ACCTGTTTCT ATAATAATTA GTAAATGCC	1740
AAAGTAGTGA TAGAATATTG TGGCATTGAA GTAGCCGAAA AATTGTTAGT TTTAGCATCA	1800
AAAAAGTAAA TAGATGTTGA AATGAATTTT TGTATGTGCC AGGTGAAGA GAGTGTGCCA	1860
GTGACAGGAA GTAGCTAAA AAATTAACAG TTATGGTTT AATAGGATCT GAAAGACAAT	1920
CTTTAAAGAA ATGGGAGAAA TTGGGGGTAT CAGTGAACCT ATACCAACCT CTCCTTGTAC	1980
ATAAATATGG TGATGTAGCT AGATATAAAA ATCAGTGTCT TACTGGCACC APTTACAGTT	2040
TAGAAAACAA TCTTTTCTT AAAAATGCCC ATCTGATTTC TATTTTtagg AGCTACTGG	2100
ATTGTATGT ATTTTCTTA CGTGAAAATA TATGTACTCT TCACTTTTGT TCCAGTACTA	2160
TAATTGCTCA TGCACCTTT CTCCCCTTTG AGAACATTCA GTGAAATACA ACTTCATCA	2220
AGATTTGCTC AAAGGAGAAG AATCGCATGA GTGTGAAAAG TAGATGCTCG TAGCCAGAAC	2280
AGAAAAGGTT ACACATGATC ATGGCACAGA AGATAGGAGG TTTGACTTGG TGGGCCATAA	2340
TGTTTATTAT CCTTTTGA ATAACAGGGA CCAGCAGCAG TTTCTCAGG ATAAATGCTC	2400
TACCCCACTT CTCTATGAAC AGGTGTGGG AGGCTTACTT TCCATTTTCA TATTTATACA	2460
CCTCTCTACA AAAGCAATTT TTAATGAAGG TTAGTGAAT TGTAAAAAT CTGAGAGGAA	2520
TGATGACTGG AGGTGTTTGG GTTTTTTTC TGTATTCATT TTTTAATGAG AAAAGTTTTA	2580
<del>AAATGACTAC AGGTAGACC GAAGTACTAC CTGACTATTA TAGGAGGATT CTATCTTCT</del>	<del>2640</del>
GTAAAGTAT TCACTAGCT TTCTCTGGG GAAAAAGTAC CACTTGGACA CTTAAAGGAA	2700
TTGGGATTTT TGTCTACTTT GGATAAGGCA GTTGACTTCT TAAGTAAAAG CAATAGTGTA	2760
AAATGTCATT TTGTTTGGAA TGTTAAGTGA GCAAAATAAAA AACATGTTGA AATTGTAAAA	2820
AAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA	2880
AAAAAAAAA AA	2892

## (2) INFORMATION FOR SEQ ID NO:14:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 100 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Met Ile Met Ala Gln Lys Ile Gly Gly Leu Thr Trp Trp Ala Ile Met  
 1 5 10 15  
 Phe Ile Ile Leu Phe Glu Ile Thr Gly Thr Ser Ser Ser Phe Leu Arg  
 20 25 30  
 Ile Asn Ala Leu Pro His Phe Ser Met Asn Arg Cys Gly Glu Ala Tyr  
 35 40 45  
 Phe Pro Phe Ser Tyr Leu Tyr Thr Ser Leu Gln Lys Gln Phe Leu Met  
 50 55 60  
 Lys Val Ser Gly Ile Val Lys Asn Leu Arg Gly Met Met Thr Gly Gly  
 65 70 75 80  
 Val Trp Gly Phe Phe Leu Tyr Ser Phe Phe Asn Glu Lys Ser Phe Lys  
 85 90 95  
 Cys Ser Thr Gly  
 100

## (2) INFORMATION FOR SEQ ID NO:15:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 618 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: double  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

ATTCGTTACA AACATGTTTG CATGCCTACC ATATCTCAGG CACTGGGGAT ACAGCAGATC 60  
 AAGATCCTAC CCCATGGAAC TAAAGAGGA CAGAGTACTG ACTGGAACAT ACGATGATAG 120  
 ATTTACAAAT AATGTAGCAT ACTTCTACTT CATTGTATCT TAAGTTTCTT GAAATATTGC 180  
 TACTGGAGAT TGGAAGAAA TCTTAATGTT ATGGGGTATT GTCTAAGAAG CTTTATTTTA 240  
 AAACCATCTC ATTAAATTTT GTTGCAATTT AGATAATCGT CCCCAGATGC CATGTTACCC 300  
 TAGTCAGAG TTTGGGGCTG GATAAGTTTT TGTGTAGGT GGCTATCCTG TGTTTTGTAG 360  
 GGTATTTAGC AGCATCCTGG CCTTAAACA AAAATGTTTT CAGACATTGC CAAATGTCCC 420  
 CCGAGCGGTA AAGTCACCCC CAAGTTGAGA ACCGCTCTAT ACAAAGAGCT GTTATTAGAG 480

CTAGACATTT CTGAATTGGC ATCAATTTCT ATATTGTATC CATAAACATT AGTAGCCACG 540  
 AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 600  
 AAAAAAAAAA AAAAAAAAAA 618

## (2) INFORMATION FOR SEQ ID NO:16:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 43 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Met Phe Ser Asp Ile Ala Lys Cys Pro Pro Ser Gly Lys Val Thr Pro  
 1 5 10 15  
 Lys Leu Arg Thr Ala Leu Tyr Lys Glu Leu Leu Leu Glu Leu Asp Ile  
 20 25 30  
 Ser Glu Leu Ala Ser Ile Ser Ile Leu Tyr Pro  
 35 40

## (2) INFORMATION FOR SEQ ID NO:17:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 772 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

TGCCATACAC TTCAGCAGAG TTGCAACTT CTCTTCTAAG TCTTTATCCT TCCCCAAGG 60  
 CATGCCTAGC ACAGGACTCT TGAACAGTGA TGCCTCAATT AGAGTTGCTA GCCAATAGAT 120  
 TGAAGCTATG TTGGCACAAT ATCCTACATC CTCCCGATCT ACTGGCTGAG CCCAACCCCA 180  
 CCTAAGAAGG ACAATAAAGA TCTGTGTTCA GAGTCATACT GAATAGAGAC TTCTGGACTC 240  
 TATAGAACCC ACTGCCTCCT GATGAAGTCC CTA CTGTGTTCA CCCTTGCAGT TTTTATGCTC 300



WO 98/37094

PCT/US98/03595

CTGGCCCAAT TGGTCTCAGG TAATTGGTAT GTGAAAAAGT GTCTAAACGA CGTTGGAATT 360  
TGCAAGAAGA AGTGCAAACC TGAAGAGATG CATGTAAAGA ATGGTTGGGC AATGTGCGGC 420  
AAACAAAGGG ACTGCTGTGT TCCAGCTGAC AGACGTGCTA ATTATCCTGT TTTCTGTGTC 480  
CAGACAAAGA CTACAAGAAT TTCAACAGTA ACAGCAACAA CAGCAACAAC AACTTTGATG 540  
ATGACTACTG CTTCGATGTC TTCGATGGCT CCTACCCGTT TCTCCCACTG GTTGAACATT 600  
CCAGCCTCTG TCTCCTGCTC TAGGATCCCC GACTCATTAA AGCAAAGAGG CTTAACAAAA 660  
AAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 720  
AAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AA 772

(2) INFORMATION FOR SEQ ID NO:18:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 131 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Met Lys Ser Leu Leu Phe Thr Leu Ala Val Phe Met Leu Leu Ala Gln  
1 5 10 15  
Leu Val Ser Gly Asn Trp Tyr Val Lys Lys Cys Leu Asn Asp Val Gly  
20 25 30  
Ile Cys Lys Lys Lys Cys Lys Pro Glu Glu Met His Val Lys Asn Gly  
35 40 45  
Trp Ala Met Cys Gly Lys Gln Arg Asp Cys Cys Val Pro Ala Asp Arg  
50 55 60  
Arg Ala Asn Tyr Pro Val Phe Cys Val Gln Thr Lys Thr Thr Arg Ile  
65 70 75 80  
Ser Thr Val Thr Ala Thr Thr Ala Thr Thr Leu Met Met Thr Thr  
85 90 95  
Ala Ser Met Ser Ser Met Ala Pro Thr Arg Phe Ser His Trp Leu Asn  
100 105 110  
le Pro Ala Ser Val Ser Cys Ser Arg Ile Pro Asp Ser Leu Lys Gln  
115 120 125

Arg Gly Leu  
130

## (2) INFORMATION FOR SEQ ID NO:19:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 875 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: double  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

CGTGTTTTCA ATATTTTATA ATGAAAATTT TTGAACATTC GGAGAAGTTG AAAGAATTAC	60
ACCCAGAACA CCCATGTCTA CCATGTTACT ACATTTGTGT GTGTGTGTGT GTGTGTGTGT	120
GTGTGCGTGT GCAATTTTAA TTACAATGGT CGAGGAAGCT CTTGCTGAGA AGGTGATGTT	180
GAATAAAGAC TCTAAAGACC CTAAAGAGTT GAGAGAGAGC TGTGTGGAGT TCTGGGGCCC	240
AGGCACAGCA AGTACAAAGA TCCTGAAGCA GGAGCATTCT TGGTGTGTTC AAGGAAAGCA	300
AGGAGGCCAG TGAGGTTGGA AAAGGGAATG AGGTCAGART AATAATAGGG TGAAAGARGA	360
TGGCTGGGGG ATGGGGGGGC ARTGARGCAG GGCCTATGGT TTCTACTTGG TGARGTGGGA	420
ARCCACTGGA RGGGTTTAAG CCGATAATTG ATGTCACATA ATTTATGTTG TAATGGAACC	480
CGTGTGACTG CTCCTGGGGA ACAGACAAAA GAAAGGGTAG TAGAGACACC AGCTAGGAAG	540
CAGATTCAGC TAGAAGAGAT GATACCTTCC ACTAAGGTGT TGGAGAAGTG GTTGGATTCT	600
AGATAATTTT TGAAGGTGGA GTTTCAGAA TTTGAAGATC ATTCCATTTC TGTTTCATACA	660
GAGCTTCCTC ATTCTCTTTT GACAGCTGCC TAGAATCTCA TTGTATCATA ATGTTTTAAA	720
CTAGTCCCCG ATGATGAATA TTTAGGTTGA TGCTTTCTCT CTTGCTGCCA CAAAACAGAC	780
ATATATTGT ATAAATGCC ACGTGGACAT GTCATTCTTC ACATAAGTGA GTATTGTAG	840
AATAAATTCC AAGAAGCAGA AAAAAAAAAA AAAAA	875

## (2) INFORMATION FOR SEQ ID NO:20:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 79 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

```

Met Ser Thr Met Leu Leu His Leu Cys Val Cys Val Cys Val Cys Val
1           5           10           15
Cys Ala Cys Ala Ile Leu Ile Thr Met Val Glu Glu Ala Leu Ala Glu
20           25           30
Lys Val Met Leu Asn Lys Asp Ser Lys Asp Pro Lys Glu Leu Arg Glu
35           40           45
Ser Cys Val Glu Phe Trp Gly Pro Gly Thr Ala Ser Thr Lys Ile Leu
50           55           60
Lys Gln Glu His Ser Trp Cys Val Gln Gly Lys Gln Gly Gly Gln
65           70           75

```

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

- (A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

TNCACGATGCC CAGTGCAAGC AGGACCAC

29

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

- (A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

TNGGACAAGGG TGTGTGAGCA GGGATGAT

29

## (2) INFORMATION FOR SEQ ID NO:23:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 29 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: other nucleic acid
  - (A) DESCRIPTION: /desc = "oligonucleotide"

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

GNGCTTCCTTC CCAGTGAATA GGTCTGT

29

## (2) INFORMATION FOR SEQ ID NO:24:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 29 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: other nucleic acid
  - (A) DESCRIPTION: /desc = "oligonucleotide"

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

ANAACTCGGT TGTGCTGTAG ATTTGTAG

29

## (2) INFORMATION FOR SEQ ID NO:25:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 29 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: other nucleic acid
  - (A) DESCRIPTION: /desc = "oligonucleotide"

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

ANGAACTAGAG GCAAGAGCAG CAGAGACC

29

## (2) INFORMATION FOR SEQ ID NO:26:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: other nucleic acid

- (A) DESCRIPTION: /desc = "oligonucleotide"

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

ANCTCTTTCCT GATTCAACAC ATTCCTCG

29

## (2) INFORMATION FOR SEQ ID NO:27:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: other nucleic acid

- (A) DESCRIPTION: /desc = "oligonucleotide"

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

CNCTCATGCGA TTCTTCTCCT TTGAGCAA

29

## (2) INFORMATION FOR SEQ ID NO:28:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: other nucleic acid

- (A) DESCRIPTION: /desc = "oligonucleotide"

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

ANCTCTGCACT AGGGAACAT GGCATCTG

29

## (2) INFORMATION FOR SEQ ID NO:29:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 29 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: other nucleic acid
  - (A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

GNGTGAACAGT AGGGACTTCA TCAGGAGG

29

(2) INFORMATION FOR SEQ ID NO:30:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 29 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: other nucleic acid
  - (A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

ANTGTAGTAAC ATGGTAGACA TGGGTGTT

29

What is claimed is:

1. An isolated polynucleotide selected from the group consisting of:
  - (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1;
  - (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 65 to nucleotide 1270;
  - (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 1139 to nucleotide 1270;
  - (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 1011 to nucleotide 1216;
  - (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BO114\_1 deposited under accession number ATCC 98333;
  - (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BO114\_1 deposited under accession number ATCC 98333;
  - (g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BO114\_1 deposited under accession number ATCC 98333;
  - (h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BO114\_1 deposited under accession number ATCC 98333;
  - (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2;
  - (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity, the fragment comprising the amino acid sequence from amino acid 196 to amino acid 205 of SEQ ID NO:2;
  - (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;
  - (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and
  - (m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

2. The polynucleotide of claim 1 wherein said polynucleotide is operably linked to at least one expression control sequence.
3. A host cell transformed with the polynucleotide of claim 2.
4. The host cell of claim 3, wherein said cell is a mammalian cell.
5. A process for producing a protein encoded by the polynucleotide of claim 2, which process comprises:
  - (a) growing a culture of the host cell of claim 3 in a suitable culture medium; and
  - (b) purifying said protein from the culture.
6. A protein produced according to the process of claim 5.
7. The protein of claim 6 comprising a mature protein.
8. A protein comprising an amino acid sequence selected from the group consisting of:
  - (a) the amino acid sequence of SEQ ID NO:2;
  - (b) the amino acid sequence of SEQ ID NO:2 from amino acid 326 to amino acid 384;
  - (c) fragments of the amino acid sequence of SEQ ID NO:2 comprising the amino acid sequence from amino acid 196 to amino acid 205 of SEQ ID NO:2; and
  - (d) the amino acid sequence encoded by the cDNA insert of clone BO114\_1 deposited under accession number ATCC 98333;the protein being substantially free from other mammalian proteins.
9. The protein of claim 8, wherein said protein comprises the amino acid sequence of SEQ ID NO:2.
10. The protein of claim 8, wherein said protein comprises the amino acid sequence of SEQ ID NO:2 from amino acid 326 to amino acid 384.



11. A composition comprising the protein of claim 8 and a pharmaceutically acceptable carrier.
12. A method for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition of claim 11.
13. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:1.
14. An isolated polynucleotide selected from the group consisting of:
  - (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3;
  - (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 418 to nucleotide 582;
  - (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 508 to nucleotide 582;
  - (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 1 to nucleotide 555;
  - (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CD311\_2 deposited under accession number ATCC 98333;
  - (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CD311\_2 deposited under accession number ATCC 98333;
  - (g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CD311\_2 deposited under accession number ATCC 98333;
  - (h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CD311\_2 deposited under accession number ATCC 98333;
  - (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4;
  - (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity, the fragment comprising the amino acid sequence from amino acid 22 to amino acid 31 of SEQ ID NO:4;

- (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;
  - (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and
  - (m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).
15. A protein comprising an amino acid sequence selected from the group consisting of:
- (a) the amino acid sequence of SEQ ID NO:4;
  - (b) the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 46;
  - (c) fragments of the amino acid sequence of SEQ ID NO:4 comprising the amino acid sequence from amino acid 22 to amino acid 31 of SEQ ID NO:4; and
  - (d) the amino acid sequence encoded by the cDNA insert of clone CD311\_2 deposited under accession number ATCC 98333;
- the protein being substantially free from other mammalian proteins.
16. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:3.
17. An isolated polynucleotide selected from the group consisting of:
- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5;
  - (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 191 to nucleotide 1756;
  - (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 254 to nucleotide 1756;
  - (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 1 to nucleotide 604;
  - (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CG279\_1 deposited under accession number ATCC 98333;
  - (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CG279\_1 deposited under accession number ATCC 98333;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CG279\_1 deposited under accession number ATCC 98333;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CG279\_1 deposited under accession number ATCC 98333;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity, the fragment comprising the amino acid sequence from amino acid 256 to amino acid 265 of SEQ ID NO:6;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

18. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:6;

(b) the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 138;

(c) fragments of the amino acid sequence of SEQ ID NO:6 comprising the amino acid sequence from amino acid 256 to amino acid 265 of SEQ ID NO:6; and

(d) the amino acid sequence encoded by the cDNA insert of clone CG279\_1 deposited under accession number ATCC 98333;

the protein being substantially free from other mammalian proteins.

19. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:5.

20. An isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 226 to nucleotide 948;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 1128 to nucleotide 1601;
- (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CJ424\_9 deposited under accession number ATCC 98333;
- (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CJ424\_9 deposited under accession number ATCC 98333;
- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CJ424\_9 deposited under accession number ATCC 98333;
- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CJ424\_9 deposited under accession number ATCC 98333;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:8;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity, the fragment comprising the amino acid sequence from amino acid 115 to amino acid 124 of SEQ ID NO:8;
- (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
- (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and
- (l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

21. A protein comprising an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:8;

- (b) fragments of the amino acid sequence of SEQ ID NO:8 comprising the amino acid sequence from amino acid 115 to amino acid 124 of SEQ ID NO:8; and
  - (c) the amino acid sequence encoded by the cDNA insert of clone CJ424\_9 deposited under accession number ATCC 98333;
- the protein being substantially free from other mammalian proteins.
- 22. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:7.
  - 23. An isolated polynucleotide selected from the group consisting of:
    - (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9;
    - (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 137 to nucleotide 895;
    - (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 1488 to nucleotide 2274;
    - (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CR930\_1 deposited under accession number ATCC 98333;
    - (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CR930\_1 deposited under accession number ATCC 98333;
    - (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CR930\_1 deposited under accession number ATCC 98333;
    - (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CR930\_1 deposited under accession number ATCC 98333;
    - (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:10;
    - (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity, the fragment comprising the amino acid sequence from amino acid 121 to amino acid 130 of SEQ ID NO:10;
    - (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

24. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:10;

(b) fragments of the amino acid sequence of SEQ ID NO:10 comprising the amino acid sequence from amino acid 121 to amino acid 130 of SEQ ID NO:10; and

(c) the amino acid sequence encoded by the cDNA insert of clone CR930\_1 deposited under accession number ATCC 98333;

the protein being substantially free from other mammalian proteins.

25. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:9.

26. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 494 to nucleotide 973;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 611 to nucleotide 973;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 521 to nucleotide 940;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone DA306\_4 deposited under accession number ATCC 98333;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone DA306\_4 deposited under accession number ATCC 98333;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone DA306\_4 deposited under accession number ATCC 98333;

- (h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone DA306\_4 deposited under accession number ATCC 98333;
  - (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12;
  - (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity, the fragment comprising the amino acid sequence from amino acid 75 to amino acid 84 of SEQ ID NO:12;
  - (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;
  - (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and
  - (m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).
27. A protein comprising an amino acid sequence selected from the group consisting of:
- (a) the amino acid sequence of SEQ ID NO:12;
  - (b) the amino acid sequence of SEQ ID NO:12 from amino acid 11 to amino acid 149;
  - (c) fragments of the amino acid sequence of SEQ ID NO:12 comprising the amino acid sequence from amino acid 75 to amino acid 84 of SEQ ID NO:12; and
  - (d) the amino acid sequence encoded by the cDNA insert of clone DA306\_4 deposited under accession number ATCC 98333;
- the protein being substantially free from other mammalian proteins.
28. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:11.
29. An isolated polynucleotide selected from the group consisting of:
- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13;
  - (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 2295 to nucleotide 2594;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 1867 to nucleotide 2372;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone DG76\_1 deposited under accession number ATCC 98333;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone DG76\_1 deposited under accession number ATCC 98333;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone DG76\_1 deposited under accession number ATCC 98333;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone DG76\_1 deposited under accession number ATCC 98333;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:14;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity, the fragment comprising the amino acid sequence from amino acid 45 to amino acid 54 of SEQ ID NO:14;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

30. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:14;

(b) the amino acid sequence of SEQ ID NO:14 from amino acid 1 to amino acid 26;

(c) fragments of the amino acid sequence of SEQ ID NO:14 comprising the amino acid sequence from amino acid 45 to amino acid 54 of SEQ ID NO:14; and



(d) the amino acid sequence encoded by the cDNA insert of clone DG76\_1 deposited under accession number ATCC 98333; the protein being substantially free from other mammalian proteins.

31. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:13.
32. An isolated polynucleotide selected from the group consisting of:
  - (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15;
  - (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 394 to nucleotide 522;
  - (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 1 to nucleotide 476;
  - (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone DO19\_1 deposited under accession number ATCC 98333;
  - (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone DO19\_1 deposited under accession number ATCC 98333;
  - (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone DO19\_1 deposited under accession number ATCC 98333;
  - (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone DO19\_1 deposited under accession number ATCC 98333;
  - (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16;
  - (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity, the fragment comprising the amino acid sequence from amino acid 16 to amino acid 25 of SEQ ID NO:16;
  - (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
  - (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

33. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:16;

(b) the amino acid sequence of SEQ ID NO:16 from amino acid 1 to amino acid 27;

(c) fragments of the amino acid sequence of SEQ ID NO:16 comprising the amino acid sequence from amino acid 16 to amino acid 25 of SEQ ID NO:16; and

(d) the amino acid sequence encoded by the cDNA insert of clone DO19\_1 deposited under accession number ATCC 98333;

the protein being substantially free from other mammalian proteins.

34. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:15.

35. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID

~~NO:17~~

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 262 to nucleotide 654;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 322 to nucleotide 654;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 1 to nucleotide 618;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone EQ219\_1 deposited under accession number ATCC 98333;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone EQ219\_1 deposited under accession number ATCC 98333;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone EQ219\_1 deposited under accession number ATCC 98333;

- (h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone EQ219\_1 deposited under accession number ATCC 98333;
  - (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:18;
  - (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 having biological activity, the fragment comprising the amino acid sequence from amino acid 60 to amino acid 69 of SEQ ID NO:18;
  - (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;
  - (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and
  - (m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).
36. A protein comprising an amino acid sequence selected from the group consisting of:
- (a) the amino acid sequence of SEQ ID NO:18;
  - (b) the amino acid sequence of SEQ ID NO:18 from amino acid 1 to amino acid 119;
  - (c) fragments of the amino acid sequence of SEQ ID NO:18 comprising the amino acid sequence from amino acid 60 to amino acid 69 of SEQ ID NO:18; and
  - (d) the amino acid sequence encoded by the cDNA insert of clone EQ219\_1 deposited under accession number ATCC 98333;
- the protein being substantially free from other mammalian proteins.
37. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:17.
38. An isolated polynucleotide selected from the group consisting of:
- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19;
  - (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 74 to nucleotide 310;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 125 to nucleotide 310;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 1 to nucleotide 338;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone FG340\_1 deposited under accession number ATCC 98333;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone FG340\_1 deposited under accession number ATCC 98333;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone FG340\_1 deposited under accession number ATCC 98333;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone FG340\_1 deposited under accession number ATCC 98333;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:20;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:20 having biological activity, the fragment comprising the amino acid sequence from amino acid 34 to amino acid 43 of SEQ ID NO:20;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

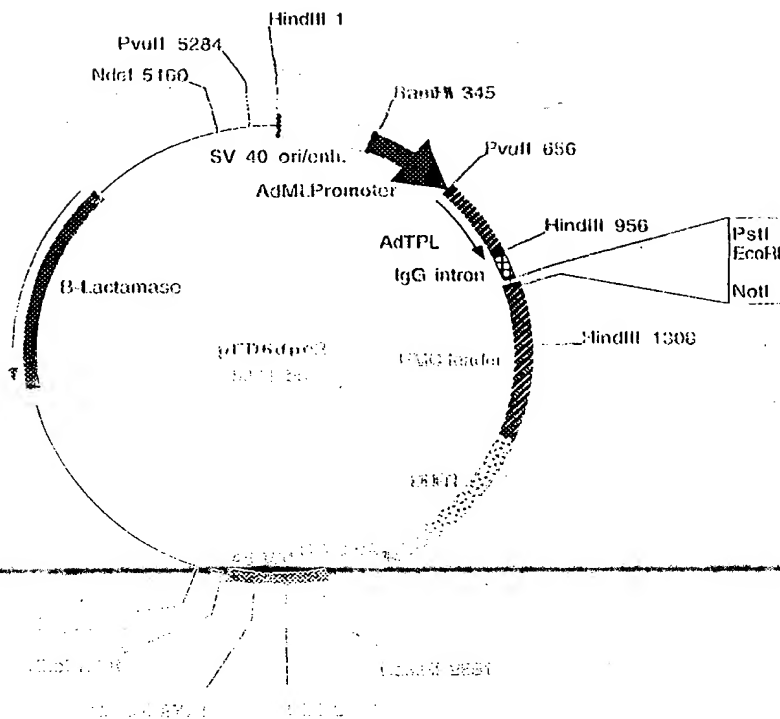
39. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:20;

(b) the amino acid sequence of SEQ ID NO:20 from amino acid 1 to amino acid 75;

- (c) fragments of the amino acid sequence of SEQ ID NO:20 comprising the amino acid sequence from amino acid 34 to amino acid 43 of SEQ ID NO:20; and
- (d) the amino acid sequence encoded by the cDNA insert of clone FG340\_1 deposited under accession number ATCC 98333; the protein being substantially free from other mammalian proteins.
40. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:19.

FIGURE 1A

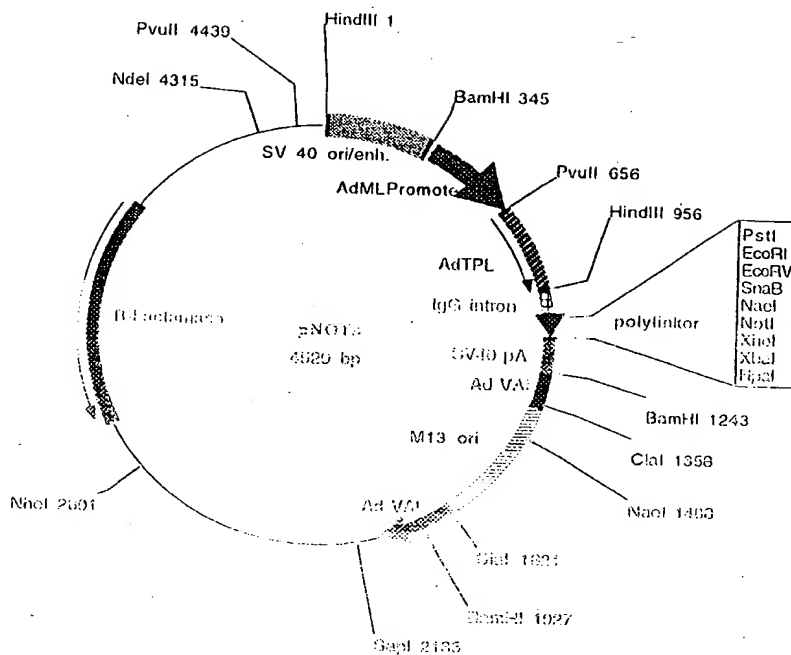


Plasmid name: pED6dpc2

Plasmid size: 5074 bp

**Comments/References:** pED6dpc2 is derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning. SST cDNAs are cloned between EcoRI and NotI. pED vectors are described in Kaufman et al.(1993), NAR 19: 4485-4490.

FIGURE 1B



Plasmid name: pNOTs

Plasmid size: 4529 bp

Comments/References: pNOTs is a derivative of pMT2 (Kaufman et al, 1989, Mol. Cell. Biol. 9:1741-1750). DHFR was deleted and a new polylinker was inserted between EcoRI and HpaI. M13 origin of replication was inserted in the Clal site. SSF cDNAs are cloned between EcoRI and NotI

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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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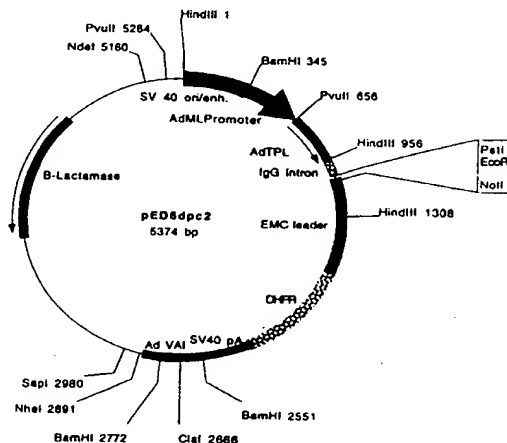
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(57) Abstract

Novel polynucleotides and the proteins encoded thereby are disclosed.



Plasmid name: pED6dpc2

Plasmid size: 5374 bp

Comments/References: pED6dpc2 is derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning. SST cDNAs are cloned between EcoRI and NotI. pED vectors are described in Kaufman et al. (1991), NAR 19: 4485-4490.

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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 98/03595

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/12 C12N5/10 C07K14/47 C12Q1/68 A61K38/17

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07K C12Q A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	L. HILLIER ET AL.: "The WashU-Merck EST Project" EMBL SEQUENCE DATABASE, 1 March 1995, XP002064960 HEIDELBERG, FRG yb37g07.sl Homo sapiens cDNA clone 73404, Accession no. T55811 ---	1
X	L. HILLIER ET AL.: "The WashU-Merck EST Project" EMBL SEQUENCE DATABASE, 2 July 1995, XP002064961 HEIDELBERG, FRG yn50b11.rl Homo sapiens cDNA clone 171837 5' similar to contains PTR5 repetitive element, Accession no. H19258 --- -/-	1

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

18 May 1998

Date of mailing of the international search report

27.08.1998

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# INTERNATIONAL SEARCH REPORT

Intern. Appl. No.  
PCT/US 98/03595

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ADAMS M D ET AL: "3,400 NEW EXPRESSED SEQUENCE TAGS IDENTIFY DIVERSITY OF TRANSCRIPTS IN HUMAN BRAIN" NATURE GENETICS, vol. 4, no. 3, pages 256-267, XP000611495 see the whole document	1-13
A	JACOBS K ET AL: "A NOVEL METHOD FOR ISOLATING EUKARYOTIC CDNA CLONES ENCODING SECRETED PROTEINS" JOURNAL OF CELLULAR BIOCHEMISTRY - SUPPLEMENT, vol. 21A, 10 March 1995, page 19 XP002027246 see abstract	1-13
A	EP 0 510 691 A (OSAKA BIOSCIENCE INST) 28 October 1992 see the whole document	1-13
A	WO 94 07916 A (MERCK & CO INC ;SCHMIDT AZRIEL (US); RODAN GIDEON A (US); RUTLEDGE) 14 April 1994 see the whole document	1-13
A	WO 90 05780 A (OREGON STATE) 31 May 1990 see the whole document	1-13
A	WO 90 14432 A (GENETICS INST.) 29 November 1990 see the whole document	1-13
A	WO 96 17925 A (IMMUNEX CORP) 13 June 1996 see the whole document	1-13
A	R.J. KAUFMAN ET AL.: "Effect of von Willebrand factor coexpression on the synthesis and secretion of factor VIII in chinese hamster ovary cells" MOL. CELL. BIOL., vol. 9, no. 3, March 1989, pages 1233-1242, XP002041592 ASM WASHINGTON, DC,US see the whole document	1-13
A	R.J. KAUFMAN ET AL.: "The phosphorylation state of eucaryotic initiation factor 2 alters translation efficiency of specific mRNAs" MOL. CELL. BIOL., vol. 9, no. 3, March 1989, pages 946-958, XP002041593 ASM WASHINGTON, DC,US see the whole document	1-13

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/03595

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	R.J. KAUFMAN ET AL.: "Improved vectors for stable expression of foreign genes in mammalian cells by use of the untranslated leader sequence from EMC virus" NUCLEIC ACIDS RESEARCH, vol. 19, no. 16, 1991, pages 4485-4490, XP002041594 IRL PRESS LIMITED, OXFORD, ENGLAND cited in the application see the whole document ---	1-13
A	US 5 536 637 A (JACOBS KENNETH) 16 July 1996 cited in the application see the whole document ---	1-13
P,A	WO 97 07198 A (GENETICS INSTITUT) 27 February 1997 see the whole document ---	1-13
P,A	WO 97 25427 A (GENETICS INST) 17 July 1997 see the whole document ---	1-13
P,X	L. HILLIER ET AL.: "The WashU-Merck EST Project" EMBL SEQUENCE DATABASE, 25 May 1997, XP002064962 HEIDELBERG, FRG cited in the application zw20e04.rl Soares ovary tumor NbHOT Homo sapiens cDNA clone 769854 5' similar to contains element MER22 repetitive element -----	1

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/ 03595

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claim 12 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see continuation sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-13

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

## 1. Claims: 1-13

An isolated polynucleotide selected from the group consisting of: SEQ ID no.1; said polynucleotide wherein said polynucleotide is operably linked to an expression control sequence; a host cell transformed with said polynucleotide; a process for producing a protein which is encoded by said polynucleotide sequence; a protein comprises an amino acid sequence selected from the group of SEQ ID no.2, a composition comprising said protein and a pharmaceutical acceptable carrier; a method for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of said composition; an isolated gene corresponding to the cDNA sequence of SEQ ID no.1.

## 2. Claims: 14-16

An isolated polynucleotide sequence selected from the group of SEQ ID no.3; a protein comprising an amino acid sequence selected from the group of SEQ ID no.4; an isolated gene corresponding to the cDNA sequences of SEQ ID no.3;

## 3. Claims: 17-19

Idem as subject 2 but limited to SEQ ID nos.5 and 6.

## 4. Claims: 20-22

Idem as subject 2 but limited to SEQ ID nos.7 and 8.

## 5. Claims: 23-25

Idem as subject 2 but limited to SEQ ID nos.9 and 10.

## 6. Claims: 26-28

Idem as subject 2 but limited to SEQ ID nos.11 and 12.

## 7. Claims: 29-31

Idem as subject 2 but limited to SEQ ID nos.13 and 14.

## 8. Claims: 32-34

Idem as subject 2 but limited to SEQ ID nos.15 and 16.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

9. Claims: 35-37

Idem as subject 2 but limited to SEQ ID nos.17 and 18.

10. Claims: 38-40

Idem as subject 2 but limited to SEQ ID nos.19 and 20.



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/03595

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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1. Information on patent family members

PCT/US 98/03595

Form PCT/ISA/210 (patent family annex) (July 1992)